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Management of Trigeminal Autonomic Cephalgias and Hemicrania Continua

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Abstract

The trigeminal autonomic cephalgias (TACs) are a group of primary headache disorders characterised by unilateral trigeminal distribution pain that occurs in association with ipsilateral cranial autonomic features. This group of headache disorders includes cluster headache, paroxysmal hemicrania and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT syndrome). Although hemicrania continua has previously been classified amongst the TACs, its nosological status remains unclear. Despite their similarities, these disorders differ in their clinical manifestations and response to therapy, thus underpinning the importance of recognising them. We have outlined the clinical manifestations, differential diagnoses, diagnostic workup and the treatment options for each of these syndromes.

The trigeminal autonomic cephalgias (TACs) are a group of primary headache disorders characterised by unilateral trigeminal distribution pain that occurs in association with ipsilateral cranial autonomic features.[1] These headaches will be grouped into section 3 of the revised[2] International Headache Society (IHS) classification.[3] This review adopts the definitions of the Classification Committee as currently proposed (www.i-h-s.org). The TACs include cluster headache, paroxysmal hemicrania and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT syndrome). The nosology of hemicrania continua is unclear and we cover it for completeness, although it will be best placed in section 4 of the updated classification. Monographs have been written on these topics which have a strong historical relevance,[4,5] and a number of recent monographs[6-9] and reviews[10,11] are available for further reading.

Cluster headache, paroxysmal hemicrania and SUNCT syndrome are characterised by short-lasting

Table I. Primary short-lasting headaches[a]

Prominent autonomic features	Sparse or no autonomic features
Cluster headache	Trigeminal neuralgia
Paroxysmal hemicrania	Idiopathic stabbing headache[b]
SUNCT syndrome	Cough headache
	Benign exertional headache
	Benign sex headache[c]
	Hypnic headache

a Short lasting is taken to be generally <4h.

b Likely to be renamed primary stabbing headache when the International Headache Society classification is revised.[2]

c Likely to be renamed sexual activity headache when the International Headache Society classification is revised.[2]

SUNCT syndrome = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

headaches with autonomic features. A more comprehensive list of short-lasting headaches is provided in table I. Despite their common elements, these three TACs differ in attack duration and frequency as well as the response to therapy. Cluster headache has the longest attack duration and relatively low attack frequency. Paroxysmal hemicrania has intermediate duration and intermediate attack frequency. SUNCT syndrome has the shortest attack duration and the highest attack frequency (see table II). In contrast with these, hemicrania continua is a continuous headache and should be considered in the differential diagnosis of relatively long-lasting chronic daily headache (see table III).[12] The importance of recognising these syndromes resides in their excellent but highly selective response to treatment. Hence, early diagnosis will often lead to appropriate treatment and the rapid relief of the patient's pain problem.

1. Cluster Headache

Cluster headache is a strictly unilateral headache that occurs in association with cranial autonomic

Table II. Typical clinical features of trigeminal autonomic cephalgias (TACs) and hemicrania continua

Feature	Cluster headache	Paroxysmal hemicrania	SUNCT syndrome	Hemicrania continua
Sex F : M	1 : 3.5–7	2.13–2.36 : 1	1 : 2.1	2.4 : 1
Pain				
type	Stabbing, boring	Throbbing, boring, stabbing	Burning, stabbing, sharp	Background dull ache, throbbing/ stabbing exacerbations
severity	Excruciating	Excruciating	Moderate to severe	Moderate background pain; severe exacerbations
site	Orbit, temple	Orbit, temple	Periorbital	Orbit, temple
Attack frequency	1/alternate day–8 daily	1–40/day	1/day–30/hour	Continuous
Duration of attack	15–180 min	2–45 min	5–250 sec	Continuous background pain; exacerbations very variable lasting min to days
Autonomic features	Yes	Yes	Yes (prominent conjunctival injection and lacrimation)	Yes, mainly with exacerbations; less prominent than in other TACs
Migrainous features[a]	Yes	Yes	No	Yes, during exacerbations
Alcohol trigger	Yes	Occasional	No	Rare
Indomethacin effect		++		++
Abortive treatment	Sumatriptan injection or nasal spray	Nil	Nil	Nil
	Oxygen			
Prophylactic	Verapamil	Indomethacin	Lamotrigine	Indomethacin
treatment	Methysergide			
	Lithium			
	Prednisone or prednisolone			

a Nausea, photophobia or phonophobia.

++ indicates absolute response to indomethacin.

Table III. Classification of chronic daily headache[12]

Primary	Secondary
>4h daily	Post-traumatic
chronic migraine[a]	head injury
chronic tension-type headache[a]	iatrogenic
hemicrania continua[a]	post-infectious
new daily persistent headache[a]	Inflammatory, such as:
<4h daily	giant cell arteritis
chronic cluster headache[b]	sarcoidosis
chronic paroxysmal hemicrania	Behcet's syndrome
SUNCT	Chronic CNS infection
hypnic headache	Cranial neuralgias
	Intracranial tumour
	Substance abuse headache[a]

a May be complicated by analgesic overuse. In the case of substance abuse headache, the headache is completely resolved after the substance abuse is controlled.[3] Clinical experience suggests that many patients continue to have headache even after cessation of analgesic use. The residual headache probably represents the underlying headache biology.

b Chronic cluster headache patients may have more than 4h per day of headache. The inclusion of the syndrome here is to emphasise that, by and large, the attacks themselves are less than four hours duration.

SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

features and, in most patients, has a striking circannual and circadian periodicity. It is an excruciating syndrome and is probably one of the most painful conditions known to humans with female patients describing each attack as being worse than childbirth.

1.1 Historical Note

In 1641, Tulp gave an incomplete clinical description of a patient who probably had cluster headache.[13] Gerhard van Swieten gave a full description of a patient with episodic cluster headache in 1745.[14] Wilfred Harris' descriptions in 1926 of what he called migrainous neuralgia[15] were the first recorded of cluster headache in the English medical literature.[16] Bayard Horton's clinical description of cluster headache in 1939 was comprehensive, except for the omission of Horner's syndrome and the male predominance of the disease.[17] Horton and Harris are generally given credit for making the entity known to the medical world. Kunkle proposed the term cluster headache in 1952.[18] In 1956, Sir Charles Symonds summarised 17 cases of cluster headache in a classic paper in *Brain*.[19]

The term cluster headache is widely accepted now, although the condition was known by a large number of names (table IV), many of which reveal the perceived views about some of the pathophysiology of the condition.

1.2 Epidemiology

The prevalence of cluster headache is estimated to be 0.1%,[29] approximately the same as that of multiple sclerosis in the UK.[30] The male : female ratio is 3.5–7 : 1.[31,32] The male:female ratio has changed in case series in the last 15 years with a trend toward an increasing female preponderance; we think this is likely to be an ascertainment issue not a real shift in female incidence. Cluster headache can begin at any age, although the most common age of onset is the third or fourth decade of life.

1.3 Clinical Features

It is useful for both clinician and patient to standardise the terminology used in cluster headache. A cluster headache or attack is an individual episode of pain that can last from a few minutes to some hours. A cluster bout or period refers to the duration over which recurrent cluster attacks are occurring; it usually lasts some weeks or months. A remission is the

Table IV. Older terms for cluster headache

Erythroprosopalgia of Bing[20]
Ciliary neuralgia[21]
Migrainous neuralgia (Harris)[22]
Erythromelalgia of the head[20]
Horton's headache[23]
Histaminic cephalgia[24]
Petrosal neuralgia (Gardner) or sphenopalatine neuralgia[25]
Vidian neuralgia[26]
Sluder's neuralgia[25]
Hemicrania angioparalytica[27]
Hemicrania neuralgiformis chronica[28]
Harris-Horton's disease[23]
'A particular variety of headache'[19]

Table V. Diagnostic features of cluster headache modified from the International Headache Society (IHS)[3] with the proposed changes[2]

Cluster headache has two key forms
Episodic: occurs in periods lasting 7 days to 1 year separated by pain free periods lasting 1 month or more[a]
Chronic: attacks occur for more than 1 year without remission or with remissions lasting less than 1 month[a]
Headaches must have each of[b]
Severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes untreated
Frequency of attacks: from 1 every other day to 8 per day
Headache associated with at least one of the following signs which have to be present on the pain side
conjunctival injection
lacrimation
nasal congestion
rhinorrhoea
forehead and facial sweating
miosis
ptosis
eyelid oedema
sense of restlessness or agitation during headache[a]

a Proposed changes to IHS diagnostic criteria.[2]

b No reasonable secondary cause.

pain-free period between two cluster bouts. Cluster headache is a disorder with highly distinctive clinical features. These features are dealt with under two major headings: the cluster attack and the cluster bout.

1.3.1 The Cluster Attack

The attacks are strictly unilateral, with very few exceptions, although the headache may alternate sides. The pain is excruciatingly severe. It is located mainly around the orbital and temporal regions, although any part of the head can be affected. The headache usually lasts 45–90 minutes but can range from 15 minutes to 3 hours. It has an abrupt onset and cessation. Interictal pain or discomfort is present in some patients.[6]

The signature feature of cluster headache is the association with autonomic symptoms and it is extremely unusual for these not to be reported. The IHS classification diagnostic criteria[3] require the cluster attacks to be accompanied by at least one of the following, which have to be present on the pain side: conjunctival injection, lacrimation, miosis, ptosis, eyelid oedema, rhinorrhoea, nasal blockage, and forehead or facial sweating (see table V). The autonomic features are transient, lasting only for the duration of the attack, with the exception of partial Horner's syndrome; ptosis or miosis may rarely persist, especially after frequent attacks.

Recently, there have been descriptions of the full range of typical migrainous symptoms in significant proportions of cluster patients.[32-34] Premonitory symptoms: tiredness, yawning; associated features: nausea, vomiting, photophobia, phonophobia; and aura symptoms have all been described in relation to cluster attacks. However, in contrast to migraine, patients with cluster headache are usually restless and irritable, preferring to move about; looking for a movement or posture that may relieve the pain.[32]

The cluster attack frequency varies between one every alternate day to three daily, although some patients have up to eight daily. The condition can have a striking circadian rhythmicity, with some patients reporting that the attacks occur at the same time each day. Alcohol, nitroglycerin, exercise and elevated environmental temperature are recognised precipitants of acute cluster attacks. Alcohol induces acute attacks, usually within an hour of intake in the vast majority of patients, contrasting with migraine patients who generally have headache some hours after alcohol intake. Alcohol triggers attacks during a cluster bout but not in a remission. Allergies, food sensitivities, reproductive hormonal changes[32] and

stress do not appear to have any significant role in precipitating attacks.

1.3.2 The Cluster Bout

Cluster headache is classified according to the duration of the bout. About 80–90% of patients have episodic cluster headache, which is diagnosed when they experience recurrent bouts, each with a duration of more than a week and separated by remissions lasting more than 2 weeks. The remaining 10–20% of patients have chronic cluster headache in which either no remission occurs within 1 year or the remissions last less than 14 days. The time window to differentiate episodic and chronic will be increased to 4 weeks after the IHS classification is revised.[2]

Most patients with episodic cluster headache have one or two annual cluster periods, each lasting between 1 and 3 months. Often, a striking circannual periodicity is seen with the cluster periods, with the bouts occurring in the same month of the year. In others the cluster periods tend to recur at regular intervals that are consistently different than 12 months. Although the duration of the cluster and remission periods varies between individuals, these periods remain relatively consistent within the same individual.

1.4 Natural History

Although there is a paucity of literature on the long-term prognosis of cluster headache, the available evidence suggests that it is a lifelong disorder in the majority of patients. In one study, in about one-tenth of patients, episodic cluster headache evolved into chronic cluster headache, whereas in one-third of patients, chronic cluster headache transformed into episodic cluster headache.[35] An encouraging piece of information for individuals with cluster headache is that a substantial proportion of them can expect to develop longer remission periods as they age.[36]

1.5 Differential Diagnoses

In spite of the rather characteristic clinical picture, the diagnosis may be difficult in some patients as each of the features of cluster headache can be mimicked by other headaches (see table VI). The

Table VI. Differential diagnoses of cluster headache

Primary headache syndromes
Paroxysmal hemicrania
SUNCT syndrome
Hemicrania continua
Migraine
Hypnic headache
Secondary causes of cluster headache
Vascular causes
carotid artery dissection[37] or aneurysm[38]
vertebral artery dissection[39] or aneurysm[40]
pseudoaneurysm of intracavernous carotid artery[41]
anterior communicating artery aneurysm[38,42]
occipital lobe AVM[43]
middle cerebral artery territory AVM[44]
AVM in soft tissue of scalp above ear[45]
frontal lobe and corpus callosum AVM[46]
cervical cord infarction[47]
lateral medullary infarction[48]
frontotemporal subdural haematoma[49]
Tumours
prolactinoma[38]
pituitary adenoma[50]
parasellar meningioma[51]
sphenoidal meningioma[52,53]
epidermoid tumour in the prepontine (behind the dorsum sella turcica)[54]
tentorial meningioma[55]
high cervical meningioma[56]
nasopharyngeal carcinoma[57]
Infectious causes
maxillary sinusitis[53]
orbito-sphenoidal aspergillosis[58]
herpes zoster ophthalmicus[59]
Post-traumatic or surgery
facial trauma[6]
following enucleation of eye[60-63]
Dental causes
impacted wisdom tooth[64]
following dental extraction[65]
Secondary headache syndromes
Tolosa-Hunt syndrome
Temporal arteritis
Raeder's paratrigeminal neuralgia[66]

AVM = arteriovenous malformation; **SUNCT syndrome** = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

main differential diagnoses to consider are: (i) secondary causes of cluster headache; (ii) other trigeminal autonomic cephalgias; (iii) migraine; and (iv) hypnic headache.

Before a diagnosis of cluster headache can be made, secondary headache disorders that mimic cluster headache need to be excluded. Symptomatic cluster headache has been described after infectious, vascular and neoplastic intracranial lesions. Any atypical features in the history or abnormalities on neurological examination (with the exception of partial Horner's syndrome) warrant further investigations to search for organic causes.

Unilateral pain, and presence of migrainous and autonomic symptoms are features common to both migraine and cluster headache, and differentiating between them can be difficult in some individuals. The features that can be useful in distinguishing cluster headache from migraine include: (i) relatively short duration of headache; (ii) rapid onset and cessation; (iii) circadian periodicity; (iv) precipitation within an hour, rather than several hours, by alcohol; and (v) clustering of attacks with intervening remissions in episodic cluster headache. Clinically, the attack feature that cluster headache patients are generally agitated or restless and migraine patients tend to complain of aggravation of the pain with movement is correct for about 90% of patients with either headache type.

Hypnic headache typically occurs in aged persons and predominates in females. Patients are awakened from sleep by headaches that are frequently bilateral, but maybe unilateral, and typically not associated with autonomic features. The headaches are brief, lasting 5–180 minutes and can occur up to three times per night. Effective treatment include bedtime administration of lithium, indomethacin or caffeine.[67]

1.6 Investigations

The diagnosis of cluster headache is made entirely on the basis of a good clinical history and a detailed neurological examination. However, it is very difficult to clinically dissect cluster headache mimics (see table VI) from primary cluster headache. A magnetic resonance imaging (MRI) scan of the brain is a reasonable screening investigation.

1.7 Treatment: General Measures and Patient Education

The management of cluster headache includes offering advice on general measures to patients, treatment with abortive and preventative agents, and rarely surgery.

Patients should be advised to abstain from taking alcohol during the cluster bout. Otherwise, dietary factors seem to have little importance in cluster headache. Anecdotal evidence suggests that patients should be cautioned against prolonged exposure to volatile substances, such as solvents and oil based paints. Patients should be instructed to avoid afternoon naps as sleeping can precipitate attacks in some patients.

1.8 Treatment: Abortive Agents

The pain of cluster headache builds up very rapidly to such an excruciating intensity that most oral agents are too slowly absorbed to relieve the pain within a reasonable period of time. The most efficacious abortive agents are those that involve parenteral or pulmonary administration.

1.8.1 Triptans

Sumatriptan

Subcutaneous sumatriptan 6mg is the drug of choice in abortive treatment of a cluster attack. A randomised, placebo-controlled, double-blind, crossover study completed in 39 patients[68] showed that the severity of the headache at 15 minutes was reduced in 74% of attacks in which sumatriptan was administered as compared with 26% in which placebo was given. Thirty-six per cent of patients were pain free within 10 minutes of taking sumatriptan, as compared with 3% after placebo. Sumatriptan was well tolerated and there were no serious adverse events.

A double-blind, crossover and randomised study compared sumatriptan 6mg and 12mg with placebo in 134 patients.[69] The 12mg dose was no more

effective than the 6mg dose and was associated with more adverse effects.

Two large clinical trials have been performed to assess the effects of long-term administration of subcutaneous sumatriptan.[70,71] In one study, the safety and efficacy profile of subcutaneous sumatriptan 6mg was evaluated in 138 patients in the first 3 months of a 2-year open-label study.[70] They treated a maximum of two attacks daily each, comprising a total of 6353 attacks. Headache relief was obtained at 15 minutes for 96% of the attacks treated. There was no indication of any increase in the interval prior to response or increased frequency of attacks with long-term treatment. Adverse events were quantitatively similar to those seen in migraine trials and did not increase with frequent use of sumatriptan. In the second trial, subcutaneous sumatriptan administered over a period of up to 1 year was evaluated.[71] A total of 2031 attacks in 52 patients were studied. It was highly efficacious in 88% of the patients with no evidence of tachyphylaxis or rebound headaches. The profile of adverse events was comparable to long-term migraine trials. The overall efficacy of subcutaneous sumatriptan was reported to be approximately 8% less in patients with chronic cluster headache than in patients with episodic cluster headache.

In summary, subcutaneous sumatriptan 6mg is the drug of choice in abortive treatment of a cluster attack. It has a rapid effect and high response rate. In cluster headache, unlike migraine, subcutaneous sumatriptan can be prescribed at a frequency of twice daily, on a long-term basis if necessary without risk of tachyphylaxis or rebound. However, in this era of cost-conscious practise this may be seen as a relatively expensive approach. *We feel, given the devastating morbidity associated with this excruciating pain syndrome, that it is unethical to withhold treatment for cost reasons*. Although generally well tolerated, sumatriptan is contraindicated in patients with ischaemic heart disease or uncontrolled hypertension. Caution must be exercised in patients with cluster headache since the disorder predominates in middle-aged men, who often have risk factors for cardiovascular disease, particularly smoking.[72]

Although nasal sumatriptan is often used, it is considerably less efficacious than the subcutaneous formulation.[73-75] A randomised, placebo-controlled, double-blind, crossover study completed in 86 patients showed that the severity of the headache at 30 minutes was reduced in 56% of attacks in which sumatriptan nasal spray was administered as compared with 26% in which placebo was given.[74] In comparison, in an open-label, randomised, crossover trial 20mg nasal sumatriptan was compared with 6mg subcutaneous sumatriptan in 26 patients each of whom treated two attacks with the nasal and two attacks with the subcutaneous formulation. At 15 minutes only 13% of attacks treated with the nasal formulation had been aborted as compared with 94% treated with subcutaneous sumatriptan.[73] The inferior result in the open-label study may have been affected by the lack of blinding. Open-labelled studies in cluster headache are of dubious value, and uncertain ethics,[76] when the hypothesis is clear and testable with a properly controlled design.

Zolmitriptan

A double-blind, placebo-controlled trial compared the efficacy of oral zolmitriptan 5mg and 10mg for the treatment of acute attacks in episodic and chronic cluster headache.[77] With headache response defined as a two-point reduction on a five-point pain intensity scale, 30-minute response rates in episodic cluster headache were 29, 40 and 47% after placebo, 5mg and 10mg zolmitriptan, respectively. The difference only reached statistical significance for zolmitriptan 10mg compared with placebo. In addition, significantly more episodic cluster headache patients reported mild or no pain 30 minutes after treatment with 5 and 10mg zolmitriptan (57 and 60%, respectively) than after placebo (42%). In patients with chronic cluster headache, response rates following zolmitriptan 5mg or 10mg were not significantly different from placebo.

The efficacy of oral zolmitriptan in episodic cluster headache is modest and does not approach the efficacy or speed of subcutaneous sumatriptan or oxygen thereby rendering it of limited utility in clinical practice. It may be considered for patients who cannot tolerate subcutaneous or intranasal su-

matriptan and oxygen, or those who desire oral medications. An intranasal formulation of zolmitriptan would be appropriate for study in acute cluster headache.[78]

1.8.2 Oxygen

Normobaric Oxygen

Oxygen inhalation is an effective method which can be safely used for the acute treatment of cluster headache. Its mechanism of action remains unclear. Horton was the first to discover that 100% oxygen inhalation at the onset of attacks alleviates the cluster headache pain.[79] Friedman and Mikropoulos[80] also reported on its favourable effect. Kudrow noted a significant relief from cluster pain in 75% of 52 randomly selected outpatients treated with 100% oxygen administered through a facial mask at a rate of 7 L/min for 15 minutes.[81] Headache relief occurred in 62% of the patients within the first 7 minutes of oxygen inhalation; in 31% within 8–10 minutes and in 7% within 10–15 minutes. The best results were obtained in patients with episodic cluster headache under 50 years of age.

Oxygen at 6 L/min for 15 minutes was compared with air inhalation in a double-blind, crossover study of 19 patients.[82] Eleven patients used both gases. Nine out of 16 patients (56%) who used oxygen perceived a complete or substantial relief in 80% or more of their cluster attacks, as compared with only one of 14 patients (7%) who used air.

In summary, inhalation of 100% oxygen at 7–12 L/min is rapidly effective in relieving pain in the majority of patients. It should be inhaled continuously for 15–20 minutes via a non-rebreathing facial mask. Patients need to be informed that they should cover any apertures on the facemask. If oxygen inhalation is initiated as soon as the attack starts, it often aborts the attack rapidly and entirely,[81] although some patients find oxygen to be completely effective if taken when the pain is at maximum intensity.[83] Up to 25% of patients note that oxygen simply delays the attack for minutes to hours rather than completely aborting it.[81]

The great advantage with oxygen is that it has no established adverse effects. It can be readily combined with other abortive and preventative treatments. It can be used several times daily as opposed to subcutaneous or intranasal sumatriptan that can only be used up to a maximum of two or three times daily, respectively. The major drawback with oxygen inhalation treatment is the practical limitation imposed by the bulky equipment and, although small portable cylinders are available, most patients find these cumbersome and inconvenient. Furthermore, it forces the patient to sit still during treatment, a behaviour that is usually incompatible with the excruciating pain of cluster headache. Some patients are unable to hold the facemask against the face as skin contact worsens the pain. With long-term treatment, only a few responders seem to continue using oxygen. Gallagher et al.[84] found that 76% of patients had significant relief but only 31% stayed on oxygen for subsequent headaches. Further studies are needed to investigate patients' preferences for symptomatic treatment.

Hyperbaric Oxygen

The first case report of the effectiveness of hyperbaric oxygen as an abortive agent in cluster headaches was by Weiss.[85] Subsequently, an open-label trial of hyperbaric oxygen (1.3ATA) in 14 patients reported that 18 cluster attacks (12 spontaneous, 6 induced by sublingual nitroglycerin) resolved rapidly, with complete relief achieved within a mean of 6.2 minutes (range: 30 seconds–13 minutes).[86] A small placebo-controlled study of hyperbaric oxygen (2ATA) delivered over 30 minutes demonstrated efficacy in six of seven patients within 5–30 minutes.[87] In addition, in three of six responders the cluster bout was completely interrupted while in the other three responders the cluster bout was partially interrupted for 3–6 days. Subsequently, hyperbaric oxygen (2.5ATA) was tested as a prophylactic treatment in cluster headache. In a double-blind, placebo-controlled, crossover study in 12 patients with episodic and 4 with chronic cluster headache no significant effect was obtained.[88]

In summary, hyperbaric oxygen appears to be effective as an abortive agent in cluster headache, which is not surprising considering the beneficial effect of normobaric oxygen. It would not be surprising if hyperbaric oxygen was more effective

than normobaric oxygen, although this needs to be confirmed in a properly conducted trial. With the currently available data, there is very weak evidence for a prophylactic effect of hyperbaric oxygen in cluster headache. The clinical utility of this treatment modality is likely to remain limited in the foreseeable future because of the lack of general availability and the other practical limitations already outlined for normobaric oxygen.

1.8.3 Topical Local Anaesthetics

Intranasal cocaine and lignocaine have been used in cluster headache for anaesthesia of the pterygopalatine (sphenopalatine) fossa region.

Cocaine

Intranasal cocaine has been reported to be effective at aborting nitroglycerin-induced cluster attacks in an open-label trial in ten patients.[89] The patients applied 50mg of cocaine flakes on a cotton swab in the region of the ipsilateral pterygopalatine ganglion. Nine patients experienced 80% or greater reduction in the intensity of their induced cluster headache within 2.5 minutes.

Recently, 10% cocaine (1 mL; 50mg per application) was reported to be effective at aborting nitroglycerin-induced cluster attacks in a double-blind, placebo-controlled study in nine patients.[90] Cocaine or saline was applied using a cotton swab in the area corresponding to the pterygopalatine fossa, under anterior rhinoscopy. The treatment was applied bilaterally for 5 minutes. All patients responded to intranasal cocaine with complete cessation of pain occurring after 31.3 ± 13.1 minutes.

Cocaine does not have widespread medicinal uses because of its addictive potential and lidocaine (lignocaine) is preferentially used.

Lidocaine (Lignocaine)

Kittrelle et al.[91] first reported that lidocaine solution applied topically to the region of the pterygopalatine fossa alleviated the pain of the cluster attack. In an open-label trial of intranasal lidocaine 4% solution, four of five patients obtained rapid relief of nitroglycerin-induced cluster headaches. Lidocaine was also effective in relieving spontaneous attacks. Subsequently, Hardebo and Elner[92] reported on the use of intranasal lidocaine 4% solution in an open-label trial in 19 patients. Seven patients (37%) reported a 50% or greater response; seven patients (37%) reported a response less than 50%, while five patients (26%) reported no benefit.

Robbins reported on the use of 4–6 sprays of lidocaine 4% in the nostril ipsilateral to the painful side in an open-label trial in 30 patients.[93] Eight patients (27%) reported moderate relief, eight patients (27%) obtained mild relief, and 14 patients (47%) stated that they had no relief from the lidocaine. No patient reported excellent relief. These findings were considerably poorer than those of Kittrelle et al.[91] and Hardebo and Elner.[92] This poorer efficacy reported by Robbins may, at least in part, be attributable to the formulation used; Robbins used a spray rather than the nose drops used in other studies.[94]

Recently, 10% lidocaine was reported to be effective at aborting nitroglycerin-induced cluster attacks in a double-blind, placebo-controlled study in nine patients.[90] Lidocaine or saline was applied using a cotton swab in the area corresponding to the pterygopalatine fossa, under anterior rhinoscopy. The treatment was applied bilaterally for 5 minutes. All patients responded rapidly to intranasal lidocaine with complete cessation of pain occurring after 37.0 ± 7.8 minutes. The authors partly attributed these results to bilateral application of lidocaine and to the procedure of drug administration, which involved anterior rhinoscopy. Although the 100% response rate appears to be excellent, the stated mean time to cessation of pain is unacceptably long for the majority of patients.

We use lidocaine solution 20–60mg, given as nasal drops (4–6% lignocaine solution) and applied bilaterally in the region of the pterygopalatine fossa. The patient needs to be instructed carefully on the self-administration of intranasal lidocaine by a nasal dropper. To ensure that the solution reaches the pterygopalatine foramen, the patient should be instructed to lie down horizontally as early as possible during an attack, with the head extending out of the bed, bent downwards 30–45° and rotated 20–30° towards the side of the headache. The tip of the

dropper is inserted above the rostral end of the inferior turbinate and pushed inwards as deep as possible before dripping. The patient should be asked to maintain the position for about 2–5 minutes. An alternative method of application is peg-pushing; a cotton swab on a peg is drowned in lidocaine before being applied to the region of the ipsilateral pterygopalatine foramen. However, peg-pushing is often reported by patients to considerably worsen the pain of cluster headache and, therefore, most patients are unable to perform the procedure accurately. In our experience, intranasal lidocaine results in mild to moderate relief in some patients, although only a few patients obtain complete pain relief (unpublished observations). Therefore, intranasal lidocaine serves as a useful adjunct to other abortive treatments but is rarely adequate on its own.

1.8.4 Ergot Deriviatives

Ergotamine

Although Horton is usually given credit for first using ergotamine in the abortive treatment of cluster headache, it was in fact Harris who first advocated its use in 1937.[15,95] Horton first described the beneficial effect of intravenous ergotamine in the abortive treatments of cluster headaches in a case reported in 1941.[96] Subsequently, Kunkle et al.[18] reported the rapid termination of cluster attacks in four patients with intravenous ergotamine. Horton et al.[97] reported 'excellent' results in open-label use of oral ergotamine tartrate 1mg/caffeine 100mg in 10 out of 14 patients. A subsequently published open trial of ergotamine 1mg/caffeine 100mg suppositories reported a considerably lower response rate of 4 out of 20 patients.[98] Friedman and Mikropoulos[80] reported that oral, suppository or intravenous preparations of ergotamine were 'effective to a greater or lesser extent' in 30 out of 35 patients.

Kudrow[81] noted a significant relief from cluster pain in 70% of 50 randomly selected out-patients treated with sublingual ergotamine at 15 minutes in a cross-over study with 100% oxygen. The peak response to sublingual ergotamine occurred within 10–12 minutes of treatment. Oxygen was regarded as superior to ergotamine, especially since there were no complications and contra-indications to its use.

Inhaled ergotamine, used in an open-label manner, has been reported to produce an 'excellent' effect in 11 of 13 patients.[99] Another open-label study reported that inhaled ergotamine given to 12 patients produced relief from pain within 30 minutes in 71% of 114 attacks.[100] Kudrow reported that 79 out of 100 patients obtained 'significant relief' from sublingual or inhaled ergotamine preparations.[4]

There are no well-controlled trials of ergotamine in abortive treatment of cluster headaches. Inhaled, subcutaneous, intramuscular or intravenous injections of ergotamine are now not widely available. In our experience, oral or rectal ergotamine is generally too slow in onset to provide meaningful relief in a timely manner, especially when compared with the rapidity of onset of action of subcutaneous sumatriptan and high-dose oxygen. Moreover, ergotamine is a potent vasoconstrictor. It is contraindicated in patients with coronary or peripheral vascular disease, arterial hypertension, and severe disease of the liver and kidney.

Dihydroergotamine (DHE)

Parenteral dihydroergotamine (DHE) has been considered to be an effective abortive agent for cluster headaches for some time.[24,80] DHE is available in injectable and intranasal formulations. Although there are no controlled trials of injectable DHE, clinical experience has demonstrated that intravenous administration provides prompt and effective relief of cluster headache within 15 minutes.[10] However, given the frequency and the rapid peak intensity of cluster attacks, intravenous DHE is not a feasible long-term solution. The intramuscular and subcutaneous routes of administration provide slower relief, although have the advantage that they can be self-administered.

DHE nasal spray 1mg has been studied in a double-blind, placebo-controlled, crossover trial in 25 patients.[101] There was no difference in the headache frequency or duration, but the pain intensity was significantly reduced with DHE compared with placebo. The dosage used (1mg) was lower than the recommended dosage for migraine (2mg) and less

than the currently available preparations of DHE nasal spray (4mg). Therefore, DHE nasal spray at a dose of 2mg or 4mg may be more effective than 1mg, although this needs to be studied in a controlled fashion.

1.8.5 Analgesics

Opiates, non-steroidal anti-inflammatory drugs (NSAIDs) and combination analgesics have no routine role in the acute management of cluster headache. The pain of cluster headache builds up very rapidly and to such an excruciating intensity that most oral agents are too slowly absorbed to act within a reasonable period of time. Furthermore, on prolonged treatment with high dosages, problems with habituation and toxicity may develop. In one study of 60 patients, only 21% reported significant relief of pain with oral analgesics but 65% continued using analgesics despite their lack of effectiveness.[84] The authors concluded that patients with cluster headache preferred to use oral analgesics for reasons that are not solely to do with the relief of pain.

1.8.6 Other Drugs

Somatostatin

Two studies have evaluated the abortive effect of somatostatin in cluster headache. Intravenous somatostatin 25 μg/min for 20 minutes was compared with ergotamine 250μg intramuscularly or placebo in a double-blind trial comprising 72 attacks in eight patients.[102] Infusion of somatostatin reduced the maximal pain intensity and the duration of pain significantly compared with placebo, and to a degree comparable to intramuscular ergotamine.

In another randomised, double-blind study, subcutaneous somatostatin was compared with ergotamine.[103] Five patients were treated for three attacks by each of the drugs. Subcutaneous somatostatin and ergotamine were equally beneficial as regards effects on maximal pain intensity and the pain area, but somatostatin was less effective in reducing the duration of pain.

This limited evidence of the beneficial effect of somatostatin needs to be explored further in properly controlled and adequately powered studies.

Olanzapine

Olanzapine has been evaluated as a cluster headache abortive agent in an open-label trial.[104] Oral olanzapine at doses ranging from 2.5 to 10mg was administered to five patients (four with chronic cluster headache, one with episodic cluster headache). It reduced the severity of cluster pain by at least 80% in four of five patients, and two patients were rendered pain-free. The pain was typically alleviated within 20 minutes and the treatment response was reported to be consistent across multiple attacks. The only adverse effect was sleepiness. This seemingly promising result needs to be replicated in a double-blind, placebo-controlled study.

Verapamil

Verapamil has been tried as an acute intravenous treatment in 15 patients with chronic cluster headache in whom the cluster attacks were induced by nitroglycerin. Intravenous verapamil 5–7mg was administered at the peak of the pain and induced a sudden decrease of pain in some patients. No significant adverse effects were noted.

1.9 Preventative Treatments

The aim of preventative therapy is to produce a rapid suppression of attacks and to maintain that remission with minimal adverse effects until the cluster bout is over, or for a longer period in patients with chronic cluster headache. Preventative therapy in cluster headache is partly based on clinical experience as very few randomised, controlled clinical trials have been performed. The literature on prophylactic drugs in cluster headache is reviewed here.

1.9.1 Calcium Channel Antagonists

Verapamil

Verapamil was first reported to be effective as a preventative in cluster headache by Meyer and Hardenberg in 1983.[105] In an open-label trial employing verapamil at doses of 160–720 mg/day in five patients with chronic cluster headache, a reduction in the mean monthly frequency of headaches was reported in all patients. In a further open-label study employing verapamil at doses of 160–480 mg/day in 34 patients with chronic cluster headache,

79% of patients reported a decrease in frequency and severity of the headaches, although these improvements were not further qualified.[106] In another open-label trial employing verapamil at doses of 240–600 mg/day in episodic cluster headache and 120–1200 mg/day in chronic cluster headache, an improvement of more than 75% was noted in 33 of 48 (69%) patients.[107]

A double-blind, crossover trial comparing verapamil 360 mg/day to the then standard prophylactic drug lithium 900 mg/day, each given for 8 weeks, found equivalent effects in the 24 patients with chronic cluster headache who completed the trial.[108] Verapamil and lithium were superior to placebo. Verapamil caused fewer adverse effects and had a shorter latency period. A double-blind, placebo-controlled trial evaluated the efficacy of verapamil 360 mg/day over a 2-week period in 26 patients with episodic cluster headache.[109] Fourteen patients were randomised to the verapamil group, while the remaining 12 patients were treated with placebo. A statistically significant reduction in headache frequency and analgesic consumption was seen in the verapamil-treated patients, with a greater reduction in the second week of treatment. At the end of 2 weeks, 86% of the verapamil-treated group showed an improvement of >50% in daily headache frequency, while no responders were observed in the placebo group.

In summary, verapamil is the preventative drug of choice in both episodic and chronic cluster headache where the bout is sufficiently long to establish a suitable dose. Clinical experience has clearly demonstrated that higher doses than those used in cardiology indications are needed. Dosages commonly employed range from 240–960 mg/day in divided doses. Verapamil can cause heart block by slowing conduction in the atrioventricular node[110] as demonstrated by prolongation of the A-H interval.[111] Observing for PR interval prolongation on ECG can monitor potential development of heart block, although it is a coarse measure. No formal guidelines are available. After performing a baseline ECG, we start patients on 80mg three times daily and thereafter the total daily dose is increased in increments of 80mg every 10–14 days. An ECG is performed before each increment and at least 10 days after the last dose change. The dose is increased until the cluster attacks are suppressed, adverse effects intervene or the maximum dose of 960 mg/day is achieved. It is unproven clinical experience that standard preparations of verapamil are more effective than the modified-release formulations.[6,112]

Constipation is the most common adverse effect, but dizziness, ankle swelling, nausea, fatigue, hypertension and bradycardia may also occur. β-Blockers should not be given concurrently.

Nimodipine

Nimodipine has been reported to be effective as a prophylactic agent for cluster headache in several trials but is not widely used. It was first reported to be effective as a preventative agent in cluster headache by Meyer and Hardenberg.[105] A double-blind, cross-over trial comparing nimodipine 60 mg/day to nimodipine 120 mg/day, each given for 8 weeks, in eight patients with chronic cluster headache, found a reduction in the mean monthly headache frequency compared with placebo, although there was a latency of 4 weeks before the headache frequency declined. Nimodipine 60 mg/day was effective in five patients (63%), while nimodipine 120mg was effective in seven patients (88%). Subsequently an open-label trial of nimodipine at doses of 60–160 mg/day in 32 patients with chronic cluster headache reported benefit in 53% of patients, although the extent of improvement was not described.[106]

An open-label study evaluated the prophylactic effect of nimodipine 30mg four times daily after 10 days of treatment in 13 patients with episodic cluster headache.[113,114] Seven patients (54%) were completely pain-free within 10 days.

Nifedipine

Nifedipine, like verapamil and nimodipine, was first reported to be effective as a preventative agent in cluster headache by Meyer and Hardenberg.[105] In an open-label trial employing nifedipine at doses of 30–180 mg/day in eight patients with chronic cluster headache, a reduction in the mean monthly frequency of headaches was reported in all patients. Subsequently, an open-label trial of nifedipine at

doses of 30–120 mg/day in 19 patients with chronic cluster headache reported benefit in 60% of patients, although the extent of improvement was not described.[106] Nifedipine, like nimodipine, is not commonly used in the prophylaxis of cluster headache.

1.9.2 Lithium

The effectiveness of lithium in psychiatric conditions of a cyclical nature, such as manic-depressive psychosis and seasonal affective disorder, led Ekbom to try this agent in cluster headache, in view of its striking circannual and circadian periodicity.[115,116] Lithium was administered to five patients (three chronic and two episodic) in an open-label fashion. The lithium dose was adjusted until a serum lithium concentration of 0.7–1.2 mmol/L was achieved. In all three chronic cluster headache patients there was an immediate, partial remission of the headache. Withdrawal of the drug resulted in an increase in intensity and frequency of the headaches. A second period of treatment again resulted in a definite improvement. In the two episodic cluster headache patients, lithium had only a slight or no effect on the headaches.

The effectiveness of lithium was subsequently verified in several unblinded series of cluster headache patients.[117-128] Open-label trials have been reviewed.[127,129] Collectively, in over 28 clinical trials involving 468 patients, good to excellent results were found in 236 (78%) of 304 chronic cluster headache patients. The response to lithium in patients with episodic cluster headache was less robust than in chronic cluster headache, with good efficacy having been obtained in 103 (63%) of a total of 164 patients treated.

Most unblinded trials used a lithium dose ranging from 600–1200 mg/day. Lithium was often effective at serum concentrations (0.4–0.8 mEq/L) less than that usually required for the treatment of bipolar disorder. Patients who improved on lithium often showed dramatic relief within the first week.[117,118,127] Manzoni et al.[128] assessed the long-term therapeutic efficacy of lithium in 18 patients with chronic cluster headache and reported that it appears to be durable for up to 4 years after treatment. Upon interruption or cessation of lithium therapy in patients with chronic cluster headache, a transition to episodic cluster headache has been recognised.[127,128] Some patients eventually become resistant to lithium.[127]

Lithium has also been evaluated in two randomised, double-blind trials. A double-blind, cross-over trial comparing verapamil 360 mg/day to lithium 900 mg/day, each given for 8 weeks, found equivalent effects in the 24 patients with chronic cluster headache who completed the trial.[108] Verapamil and lithium were superior to placebo. A double-blind, placebo-controlled, randomised, parallel group trial of sustained release lithium 800 mg/day in 27 patients (13 on lithium, 14 on placebo) with episodic cluster headache assessed efficacy at 1 week after the start of treatment.[130] Cessation of attacks within 1 week occurred in two patients in each group, while substantial improvement was noted in 6 (43%) of 14 patients on placebo and 8 (62%) of 13 patients on lithium. Lithium treatment was associated with a subjective improvement rate but this was not statistically significant compared with the placebo group. The authors made an assumption at the onset of the trial that the placebo response would be zero. This assumption turned out to be flawed and, consequently, the study was inadequately powered to test the proposed hypothesis. Hitherto, it had been assumed that placebo response in prophylactic studies of cluster headache was insubstantial. This is clearly incorrect for both acute attack and preventative treatment approaches in cluster headache.[131]

In summary, lithium is an effective agent for cluster headache prophylaxis, although the response is less robust in episodic cluster headache than chronic cluster headache. Most patients will benefit from dosages of 600–1200 mg/day. Lithium has the potential for many adverse effects and has a narrow therapeutic window. Adverse effects of lithium include weakness, nausea, thirst, tremor, slurred speech and blurred vision. Toxicity is manifested by nausea, vomiting, anorexia, diarrhoea, and neurological signs of confusion, nystagmus, ataxia, extrapyramidal signs and seizures. Hypothyroidism and polyuria (nephrogenic diabetes insipidus) can occur

with long-term use. Polymorphonuclear leukocytosis may occur and be mistaken for occult infection. Renal and thyroid function tests are performed before and during treatment. We start patients on 300mg twice daily and the dose is thereafter titrated using the protocol outlined in the British National Formulary. The dose is increased until the cluster headaches are suppressed, adverse effects intervene or the serum lithium concentration is in the upper part of the therapeutic range. The serum concentrations should be measured 12 hours after the last dose and should not exceed the upper limit of the therapeutic range. The lithium dose may need to be adjusted in accordance with the spontaneous, fluctuating course of this disorder. In addition, we advise drug withdrawal at least once annually to detect the patients whose pattern of cluster headache has changed from chronic to episodic. The concomitant use of NSAIDs, diuretics and carbamazepine is contra-indicated.

1.9.3 Serotonergic Agonists and Antagonists

Methysergide

Methysergide is an ergot alkaloid, which is an antagonist at serotonin $5HT_{2A}$, $5HT_{2B}$ and $5HT_{2C}$ receptors, and an agonist at $5HT_{1B/1D}$ receptors.

Methysergide was first reported to be effective in cluster headache by Sicuteri.[132] Subsequently, several authors confirmed this observation in open-label trials of this agent.[133-139] The open-trials were reviewed by Curran et al.[140] who noted that methysergide, used at 3–12 mg/day, was effective in 329 (73%) of 451 patients with episodic and chronic cluster headache.

Subsequently, Kudrow reported that, in open-label use, methysergide was effective in 50 (65%) of 77 patients with episodic cluster headache and 3 (20%) of 15 patients with chronic cluster headache, but the drug appears to lose its effectiveness with repeated use in up to 20% of patients.[4] However, Krabbe[141] reported a limited prophylactic benefit with methysergide, used in an open-label manner, in both episodic and chronic cluster headache. The efficacy of methysergide (used at up to 12 mg/day) was examined prospectively in 42 patients (16 episodic, 26 chronic). Thirteen of the 42 patients had good or excellent benefits, but two of these 13 patients had severe adverse effects. Thus, methysergide was beneficial without adverse effects in 11 (26%) of 42 patients. There was no significant difference in treatment response between the episodic (25%) and chronic (27%) groups. In addition, a retrospective analysis of 164 patients treated with methysergide demonstrated a satisfactory effective in only 44 (27%).[141]

In summary, methysergide is indicated for the treatment of cluster headaches, although the efficacy data from the open-label trials is inconsistent. Dosages of up to 12 mg/day can be used if tolerated. To minimise adverse effects, patients can start with a low dose and increase the dose gradually. We start patients on 1mg once daily and the daily dose is then increased by 1mg every 3 days (in a three times daily regimen) until the daily dose is 5mg; thereafter, the dose is increased by 1mg every 5 days. Common short-term adverse effects include nausea, vomiting, dizziness, muscle cramps, abdominal pain and peripheral oedema. Uncommon but troublesome adverse effects are caused by vasoconstriction (coronary or peripheral arterial insufficiency), which usually necessitate cessation of therapy with this drug. Prolonged treatment has been associated with fibrotic reactions (retroperitoneal, pulmonary, pleural and cardiac), although these are rare.[142] Ideally, the drug should only be used in patients with short cluster bouts, preferably less than 3–4 months. If prolonged use is intended then the risk of fibrotic reactions can be minimised by giving the drug for 6 months followed by a 1-month break before starting the drug again. To avoid a sudden increase in headache frequency when methysergide is stopped, the patient should be weaned off over 1 week. Some authorities use methysergide on a continuous basis with careful monitoring, which includes auscultation of the heart and yearly ECG, chest radiograph and abdominal MRI.[143] All patients receiving methysergide should remain under the supervision of the treating physician and be examined regularly for the development of visceral fibrosis or vascular complications.

Contraindications to the use of methysergide include pregnancy, peripheral vascular disorders, severe arteriosclerosis, coronary artery disease, severe hypertension, thrombophlebitis or cellulitis of the legs, peptic ulcer disease, fibrotic disorders, lung diseases, collagen disease, liver or renal function impairment, and valvular heart disease.[144]

Ergots, triptans and methysergide: There is a considerable issue surrounding the use of ergot derivatives and triptans with methysergide. This is not at all an easy subject. It is usually recommended that ergotamine or DHE should not be taken concomitantly with methysergide, while other vasoconstrictive agents should only be used with caution. Methysergide is an ergot derivative[145] but is a weak vasoconstrictor when compared with ergotamine.[146] It is demethylated *in vivo* to methylergonovine, to which it may owe some of its activity.[147] There are no reported prospective drug-interaction studies between methysergide and sumatriptan. In some of the early clinical studies with sumatriptan, methysergide continued to be used.[148] Eighty patients were taking either of methysergide or pizotifen, both $5HT_2$ antagonists. They had used either sumatriptan injections (n = 38) or tablets (42). There was insufficient power to analyse this group but they had a similar adverse event profile.[148] The most worrisome case report was that of a 43 year old woman who experienced a myocardial infarction while taking methysergide and sumatriptan.[149] She had a history of migraine without aura and atypical chest pain attributed to gastroesophageal reflux. She had controlled hypertension. Coronary angiography revealed a 50% block of the left anterior descending coronary artery that was treated by stenting. In retrospect sumatriptan was contraindicated in this patient because of the ischemic heart disease, although one might argue that this was a difficult diagnostic issue. For cluster headache we are unaware of any similar case. Thus, the combined use of ergot derivatives or sumatriptan with methysergide must remain a clinical decision based on the balance of the very considerable benefit, particularly for sumatriptan and DHE, and the concomitant use of methysergide, with each case judged on its merits.

Methylergometrine

Methysergide is metabolised to an active metabolite, methylergometrine.[150] In an observational, retrospective study, methylergometrine at a dose of 0.6–0.8 mg/day was reported to be effective as an adjunctive prophylactic therapy. The drug was administered to 20 patients with episodic cluster headache who had failed to respond despite at least a 1-week trial of conventional prophylactic treatment. The authors reported decreased headache frequency in 19 (95%) patients and decreased headache intensity in 15 (75%) patients within 1 week of initiating therapy with methylergometrine.

Ergotamine

Ekbom first reported the use of ergotamine tartrate for the prophylactic treatment of cluster headaches in 1947.[23] Sixteen patients were given ergotamine at the dose of 2–3 mg/day for 1–4 weeks, and 13 patients were considerably improved. Later it was reported that a rectal suppository of ergotamine 2mg and caffeine 100mg or intramuscular injections in doses of 0.25–0.5mg at bedtime were effective in preventing nocturnal attacks.[19] Ergotamine was widely used as the first choice prophylaxis until the efficacy of lithium and verapamil became evident.

Regular administration of ergotamine 2–4 mg/day for 2–3 weeks may be useful. If the patient has nocturnal attacks, 1–2mg may be given at night in the form of tablets or suppositories. If the pattern of attacks is predictable, the dose can be given 30–60 minutes before the expected attacks. The medication needs to be carefully monitored so that the total weekly dose is not too large.

DHE

Repetitive intravenous DHE administered in an inpatient setting over a period of 3 days has been reported to be very useful in some patients with both episodic and chronic cluster headache. In a study of open-label use of repetitive intravenous DHE in 54 patients with intractable cluster headache (23 episodic, 31 chronic), all patients were headache-free.[151] At 12-month follow-up, 83 and 39% of episodic and chronic cluster headache patients, respectively, remained free of headache.

Pizotifen

In 1967 Sicuteri et al.[152] were the first to report the beneficial effect of pizotifen in seven patients with cluster headache. A review of seven small studies from 1972, reported that pizotifen has only a modest effect in cluster headache prophylaxis, being effective in 21 of 56 patients with episodic or chronic cluster headache (38% responders).[153] However, in one single-blind trial of pizotifen 3 mg/day in 28 patients with episodic cluster headache, 16 participants had a beneficial response (57% responders).[154]

While widely used in Europe and Canada, pizotifen is not available in the US and is generally not held to be very useful in cluster headache.

Triptans

There is no controlled trial evidence to support the use of oral sumatriptan in cluster headache. Sumatriptan 100mg three times daily taken before the anticipated onset of an attack or at regular times does not prevent the attack and, therefore, it should not be used for cluster headache prophylaxis.[155]

Recently, two cases reports have been published where the prophylactic use of naratriptan 2.5mg twice daily completely suppressed the attacks.[156,157] A double-blind, placebo-controlled study is needed to confirm the efficacy and safety of naratriptan as a preventative drug in cluster headache. If naratriptan proves to be an effective prophylactic agent, the difference in pharmacokinetics of naratriptan and sumatriptan may explain why sumatriptan prophylaxis is ineffective; naratriptan has a long-life and improved bioavailability compared with other 5-HT receptor agonists.

1.9.4 Corticosteroids

The use of corticosteroids in cluster headache was first reported by Horton who found that cortisone at a dosage of 100 mg/day was effective in only 4 of 21 patients.[24]

The effectiveness of prednisone in stopping bouts of cluster headache was established in a double-blind trial by Jammes.[158] Couch and Ziegler reported that prednisone 10–80 mg/day employed in 19 patients with cluster headache (9 episodic, 10 chronic) provided greater than 50% relief in 14 patients (74%) and complete relief in 11 (58%) patients.[159] Recurrence of headaches was reported in 79% of patients when the prednisone dose was tapered. Kudrow reported that, of 77 patients with episodic cluster headache unresponsive to methysergide, prednisone relieved 77% and partially improved 12%.[4] Prednisone was also found to provide marked relief in 40% of patients with chronic cluster headache and was more effective than methysergide in this patient group.

In the UK prednisone has been discontinued and therefore prednisolone is used. Our experience with the open-label use of prednisolone in cluster headache is that it is highly effective, with response rates comparable to those reported for prednisone (unpublished observations).

Dexamethasone at a dose of 4mg twice daily for 2 weeks followed by 4 mg/day for one week has also been shown to be effective.[160]

In summary, corticosteroids (prednisolone or prednisone and dexamethasone) are highly efficacious and the most rapid-acting of the prophylactic agents. As in other disorders, the use of corticosteroids is contraindicated by a history of the tuberculosis or psychotic disturbance. Furthermore, caution has to be exercised in their use because of the potential for serious adverse effects. In this regard, bone-related problems with corticosteroid use have been reviewed, and the shortest course of prednisolone[161] reported to be associated with osteonecrosis of the femoral head is a 30-day course. Furthermore, courses of adrenocorticotrophic hormone have produced osteonecrosis after 16 days and dexamethasone after 7 days.[161] Thus, a tapering course of prednisone or prednisolone for 21 days is prudent, with an excess risk for bony problems occurring if more than two courses are administered per year.[161] We start patients on oral prednisolone 1mg/kg, to a maximum of 60mg, once daily for 5 days and thereafter decrease the dose by 10mg every 3 days. Prednisone can be used at the same dosage. Unfortunately, relapse almost invariably occurs as the dose is tapered. For this reason, corticosteroids are used as an initial therapy in conjunction with preventatives, until the latter are effective.

1.9.5 Anticonvulsants

Valproic Acid

Hering and Kuritzky evaluated the effectiveness of sodium valproate (valproic acid) as preventative therapy in 15 patients with cluster headache in an open-label clinical trial.[162] Thirteen patients with episodic cluster headache received sodium valproate between 600–2000 mg/day for up to 6 months and the two with the chronic subtype received 600–1200 mg/day. Sodium valproate was effective in 11 of the 15 patients (73%). In nine patients, it controlled the pain completely, and in the remaining six patients, including the two with chronic cluster headache, it afforded 72–85% improvement. Apart from mild nausea in three patients, sodium valproate was generally well tolerated.

In another open-label trial, valproate semisodium (divalproex sodium) was administered at variable doses to 26 patients with episodic or chronic cluster headache.[163] The 21 patients with chronic cluster headache received a mean daily dose of 850 mg/day for a mean of 11.1 months. The five patients with episodic cluster headache were treated at a mean dose of 826 mg/day. With prophylaxis, the 28-day cluster headache frequency decreased by a mean of 58.6 and 53.9% among patients with episodic and chronic headache, respectively. Five patients experienced adverse events of rash, hair loss, tiredness, nausea and tremor.

A retrospective study examined the clinical efficacy and safety profile of valproate semisodium (divalproex sodium) used as monotherapy and polytherapy for prophylaxis in cluster headache.[164] The authors reviewed the medical notes of 49 patients with cluster headache. Valproate semisodium 500–1500 mg/day was administered as monotherapy in 13 patients and in combination with another prophylactic treatment in 36 patients. Improvement was seen in 73% of patients (11 on monotherapy, 25 on polytherapy), although the extent of improvement was not quantified. Adverse effects were reported by 22% of patients.

Recently, El Amrani et al.[165] reported the results of a double-blind, placebo-controlled, parallel group study of sodium valproate (1000–2000 mg/day) in the prophylaxis of cluster headache. Ninety-six patients were included, 50 in the sodium valproate group (37 episodic, 11 chronic, 2 unspecified) and 46 in the placebo group (36 episodic, 6 chronic, 3 unspecified). After a 7-day run-in period, patients were treated for 2 weeks. The primary end-point was an at least 50% reduction in the number of attacks per week between the run-in period and the last week of treatment. There was no significant difference between the two groups, with improvement in 50% of the active treatment group and 62% in the placebo group. However, the two groups were imbalanced in that the mean duration of previous cluster bouts in the patients with episodic cluster headache was shorter in the placebo group (62.4 days) compared with the treatment group (78.3 days). Consequently, the high success rate observed in the placebo group was probably attributable to the spontaneous remission of the cluster bout in addition to a true placebo response. The authors concluded that no valid conclusion about the efficacy of sodium valproate in the prophylaxis of cluster headache could be drawn because of this methodological issue.

Topiramate

In an open-label study in two patients with chronic cluster headache, seven patients with episodic cluster headache and one patient with cluster-tic syndrome, treatment with topiramate was associated with rapid improvement.[166] A dosage of topiramate 50–125 mg/day shortened the cluster period duration in nine patients and the total treated cluster period duration in four patients with episodic cluster headache. Topiramate induced remission in the two patients with chronic cluster headache within 1 and 3 weeks, respectively. Only three patients reported mild adverse effects while receiving topiramate in this study.

In another open-label study in two patients with episodic and three patients with chronic cluster headache, treatment with topiramate 75–150 mg/day was effective in three (two episodic and one chronic) of the five patients; however it proved ineffective and also caused intolerable adverse ef-

fects in two patients with chronic cluster headaches taking 125 and 200 mg/day, respectively.[167]

These favourable preliminary reports need to be followed up by properly controlled studies. In the interim, topiramate appears to be a reasonable treatment option in patients with otherwise refractory cluster headache, although its use may be limited by its adverse effect profile. Somnolence, dizziness, cognitive symptoms and ataxia are commonly reported. Mood changes, psychosis, weight loss and glaucoma have been reported. Paresthesias and nephrolithiasis can occur because of the weak carbonic anhydrase inhibition of the drug. We start topiramate at low dosages (15–25 mg/day) and make small increments of 25–50mg every 5–7 days to minimise both the total daily dosage and the potential for adverse effects.

Gabapentin

Gabapentin was first reported to be effective as a prophylactic agent in two case reports of cluster headache.[168,169] Subsequently, Leandri et al.[170] tried gabapentin 900 mg/day in an open-label fashion in eight patients with episodic cluster headache and four with chronic cluster headache. All patients were pain-free within 8 days of initiating therapy. Patients with episodic cluster headache discontinued gabapentin after 60 days of treatment without recurrence of the attacks. The four patients with chronic cluster headache remain pain-free at follow-up of 4 months. The only adverse effect reported was drowsiness in two patients. This astonishingly high response rate needs to be reproduced in controlled trials.

1.9.6 Melatonin

Melatonin is a sensitive surrogate marker of circadian rhythm in humans and is under the control of the suprachiasmatic nucleus.[171] Serum melatonin levels are reduced in patients with cluster headache, particularly during a cluster bout.[172,173] On the basis of these observations, the striking circadian periodicity of cluster headache and the importance of the hypothalamus in the pathogenesis of this disorder,[174] the efficacy of melatonin has been evaluated as a prophylactic agent in cluster headache.

Leone et al.[175] performed a double-blind pilot study of melatonin versus placebo in the prophylaxis of cluster headache. Twenty patients with cluster headache (18 episodic, 2 chronic) participated in this study. Patients with episodic cluster headache entered the study between the second and tenth day of their cluster bout. After a run-in period of 1 week without prophylactic treatment, patients were randomised to receive melatonin 10mg or placebo for 2 weeks. The authors found that compared with the run-in period, there was a reduction in the mean number of daily attacks and a strong trend towards reduced analgesic consumption in the melatonin group but not in the placebo group. Five patients in the melatonin group responded to the treatment, with cessation of cluster headaches after 5 days of treatment. No patient in the placebo group responded.

Recently, Peres and Rozen[176] reported two patients with chronic cluster headache inadequately managed on verapamil 640 mg/day who were pain-free with add-on therapy of melatonin 9 mg/day. The authors concluded that melatonin could be an adjunctive treatment for cluster headache prophylaxis, although double-blind, placebo-controlled trials are necessary to confirm this assumption.

1.9.7 Greater Occipital Nerve Blockade

Anthony described the use of local anaesthetic and corticosteroid injections around the greater occipital nerve (GON) homolateral to the pain.[177] This procedure has been widely used but not subject to systematic evaluation. Recently, it was reported that of fourteen patients treated with GON injection, four had a good response, five had a moderate response and five no response.[178] We find it a variable but sometimes effective strategy that in experienced hands has almost no morbidity.

1.9.8 Other Drugs

Baclofen

Baclofen, a $GABA_B$ receptor agonist, was recently evaluated in an open-label study in nine patients with episodic cluster headache.[179] The patients received baclofen 15 mg/day for 2 days before the dose was increased to 30 mg/day. Six patients

were pain-free within 1 week; one patient was substantially better after 1 week and became pain-free by the end of the second week. The treatment was well tolerated. These results merit further investigation with a larger number of patients in a double-blind study.

Leuprorelin

The utility of leuprorelin (leuprolide), a synthetic slow-release gonadotropin-releasing hormone analogue, as a prophylactic agent in cluster headache was investigated in a single-blind, placebo-controlled, randomised, parallel study in 60 men with chronic cluster headache.[180] Thirty patients were administered a single dose of leuprorelin 3.75mg intramuscularly, while the remaining thirty patients were administered placebo. Leuprorelin was found to induce a significant decrease of pain intensity, and attack duration and frequency. The maximum effect induced by leuprorelin was a 63% decrease of the pain intensity, while the mean duration of the attacks decreased from 94 minutes/day to 9.4 minutes/day. Twelve of 30 leuprorelin recipients reported resolution of pain 70 days after drug administration, while no effect was reported in four. The remaining leuprorelin recipients reported a general benefit that increased over time. The therapeutic benefits of leuprorelin began after 10 days and peaked at 21–30 days after treatment. The mean duration of improvement was 3.25 months. At relapse, a second dose of leuprorelin induced a similar amelioration. The main adverse effect of active treatment was decrease in libido in 6 (20%) of thirty patients. Endocrinological measurements during treatment demonstrated an initial increase followed by a marked decrease of testosterone and luteinising hormone.

Intranasal Capsaicin and Civamide

Intranasal capsaicin was first reported to be beneficial as a prophylactic agent in cluster headache by Sicuteri and colleagues.[181] In this open-label preliminary study, capsaicin 300μg was applied once daily for 5 consecutive days into both nostrils of cluster headache patients. The number of spontaneously occurring attacks was significantly reduced in the 60 days after the end of capsaicin treatment. The group subsequently reported their findings in 45 patients with cluster headache (35 episodic, 10 chronic).[182] Twelve of 35 patients with episodic cluster headache received the vehicle only; this was considered as a placebo. A significant reduction in the number of attacks was observed during the observation period of 60 days. In the 23 episodic cluster headache patients treated with capsaicin, 13 (57%) had complete disappearance of the attacks while 5 (22%) had a 75% reduction in the number of attacks. Of the ten patients with chronic cluster headache, seven (70%) displayed transient benefit, being pain-free for a period of 28–40 days following treatment, while the remaining three patients derived no benefit from treatment. Intranasal capsaicin produces an intense burning sensation, lacrimation and rhinorrhoea that lasts for approximately 20 minutes (although these symptoms progressively decrease and disappear after 5–8 applications). Consequently, placebo-controlled studies are not easily performed as patients are readily unblinded.

In a double-blind, placebo-controlled study in 13 patients, seven were treated with capsaicin 0.025% twice daily for 7 days in the nostril ipsilateral to the pain while the six control patients received camphor 3% to simulate the painful irritation associated with topical capsaicin.[183] The capsaicin-treated group experienced significantly less severe headaches over the 8 days following treatment compared with the 7 days during treatment. This improvement was not observed in the placebo-treated group.

In an attempted single-blind study designed to verify the difference in efficacy of treatment with nasal capsaicin depending on the side of application, 26 patients with episodic cluster headache received capsaicin on the symptomatic side while 26 patients were treated on the non-symptomatic side.[184] Seventy percent of the patients treated on the ipsilateral side experienced a significant decrease in the number of attacks for 50–60 days after treatment compared with the attack frequency before treatment and compared with the patients treated on the non-symptomatic side. In addition, 18 patients with chronic cluster headache alternately received both ipsilateral and contralateral treatments. Application of capsai-

cin on the symptomatic side had a temporary beneficial effect in most patients, but attacks occurred within 40 days in all patients. No benefit was seen with contralateral application.

Fusco and colleagues[185] performed an open-label study to determine the reproducibility of the therapeutic effect of intranasal capsaicin. The authors carried out a 2-year follow-up study on 25 patients with cluster headache (17 episodic, 8 chronic) who had had a complete disappearance of their attacks with the first treatment of intranasal capsaicin. In the 17 patients with episodic cluster headache, seven (41%) entered a remission or had a substantial decrease of the pain attacks on further treatment, four (24%) displayed benefit with one more treatment but further repetitions did not produce appreciable results, four patients (24%) showed no benefit with repetition and two (12%) patients did not experience any bouts over the follow-up period. In the eight patients with chronic cluster headache, further treatment with intranasal capsaicin was effective in four patients but the pain-free periods lasted no longer than 40 days.

In summary, intranasal capsaicin applied ipsilateral to the symptomatic side appears to be effective in significant proportions of both episodic and chronic cluster headache patients, although the effect appears to be transient, especially in those with chronic cluster headache. In addition, a significant number of patients are refractory to repeated treatment. Finally, the intense local irritation caused by intranasal capsaicin deters patients from using this drug.

In a multicentre, vehicle controlled study patients with episodic cluster headache were treated for 7 days with either intranasal civamide 0.025% (25μg) or placebo in a volume of 100μL.[186] Eighteen patients received civamide and ten placebo and were evaluated in a 20-day post-treatment period. While the number of headaches was reduced in the first 7 days (−60% civamide vs −26% placebo), the overall effect at day 20 was not significant. Nasal burning was common in the civamide group. This is a promising approach that deserves further study.

Chlorpromazine

Caviness and O'Brien[187] administered chlorpromazine to 13 patients with cluster headache (11 episodic, 2 chronic) in an open-label fashion. In 12 (92%) of 13 patients the cluster headaches ceased completely within 2 weeks. The effective chlorpromazine dosage ranged from 75–700 mg/day. Three patients received sustained relief from cluster headaches over 6–8 months follow-up. In the other nine patients, withdrawal of chlorpromazine within 2–3 weeks was tolerated without recurrence of symptoms. Four of these patients found chlorpromazine equally effective in subsequent cluster bouts. The use of chlorpromazine for cluster headache needs to be balanced against the potential adverse effects. Tardive dyskinesia can be permanent even after a few doses, although this has only been occasionally reported. Dystonic reactions and akathisias can also occur, occasionally developing into a severe sense of restlessness or even agitation. Drowsiness occurs in many patients.

Nonetheless, this report of the effectiveness of chlorpromazine (antagonistic properties at dopaminergic and α-adrenergic receptors) as a preventative taken in conjunction with the reported effectiveness of olanzapine[104] (antagonist activity at dopaminergic $D_{1\text{-}4}$, serotonergic $5HT_{2A/2C}$, muscarinic $M_{1\text{-}5}$, histamine H_1 and α-adrenergic receptors) as an abortive agent raises the possibility that these agents mediate their effects via dopamine or, perhaps, α-adrenergic receptor antagonism. Future studies will be necessary to help determine how these agents work in cluster headache.

Transdermal Clonidine

Clonidine, an α_2-adrenergic presynaptic agonist, has been evaluated in two open-label studies. In the first study by D'Andrea et al.,[188] transdermal clonidine 5–7.5mg was administered for 1 week to eight patients with episodic and five with chronic cluster headache. The authors reported a significant reduction in the frequency, intensity and duration of attacks. Three patients with episodic cluster headache were completely pain-free and all but two patients responded. The authors reported an improvement in the first 24 hours of therapy at the dose of 5mg in the

majority of patients. The only adverse effect noted was tiredness.

Subsequently, in a study by Leone et al.,[189] transdermal clonidine 5–7.5mg was administered for 2 weeks to 16 patients with episodic cluster headache. There was no significant change in the frequency, intensity and duration of attacks. However, five patients (31%) were rendered pain-free but this improvement occurred 1 week after initiation of therapy at the dose of 5mg and coincided with an increase in dose from 5 to 7.5mg. Transdermal clonidine was very well tolerated and the only adverse effect reported was tiredness.

1.9.9 Summary

The literature on open studies is difficult to judge for various reasons: (i) in most studies measures of efficacy are not adequately defined; (ii) true response rate is impossible to determine without knowledge of the placebo response; and (iii) the remitting nature of episodic cluster headache makes it difficult to determine the true response rate. In addition, there is probably a publication bias involved in that positive results are more likely to be published than negative ones. If the true success rates were as impressive as indicated by the published results, prophylactic treatment of cluster headache would be an easy task, which it often is not.[190] With the dearth of properly controlled trials, 'evidence-based' treatment protocols are difficult to draw up. Current cluster headache prophylactic regimens are based to some extent on the data available in the literature but draw heavily on clinical experience. We outline our approach to preventative management of cluster headache in this section; it is of necessity a mixture of evidence and experience. One should be aware of the co-existence of cluster headache with trigeminal neuralgia, cluster-tic syndrome,[191-195] where both conditions need to be treated for therapeutic success.

Preventative treatments can be divided into short-term preventatives, suitable for rapidly controlling the attack frequency but not for prolonged use; and long-term therapies that are required for prolonged medical management of cluster headache (see table VII).

Short-Term Prevention

Patients with either short bouts, perhaps in weeks, or in whom one wishes to quickly control the attack frequency, can benefit from short-term prevention. These medicines are distinguished by the fact that they cannot be used in the long-term and thus may require replacement by long-term agents in many patients. Corticosteroids, methysergide and nocturnal ergotamine (for patients having only predictable nocturnal headaches) are particularly useful in this setting.

Long-Term Prevention

Some patients with either long bouts of episodic cluster headache or chronic cluster headache will require preventative treatment over many months, or

Table VII. Preventative management of cluster headache

Short-term prevention (for episodic cluster headache)	Long-term prevention (for prolonged bouts of episodic cluster headache and chronic cluster headache)
Prednisone or prednisolone (transitional only)	Verapamil
Methysergide	Lithium
Daily (nocturnal) ergotamine[a]	Methysergide
Verapamil	Valproic acid[b]
Greater occipital nerve injection[b]	Pizotifen[b]
Valproic acid (valproate semisodium)[b]	Topiramate[c]
Pizotifen[b]	Gabapentin[c]
Melatonin[b]	Melatonin[b]
Topiramate[c]	

a Patients with predictable nocturnal headaches only.

b Limited data, such as pizotifen[154] or negative data, such as valproic acid.[165]

c Unproven but promising.

even years. Verapamil and lithium are particularly useful in this setting.

1.10 Surgery

This is a last-resort measure in treatment-resistant patients and should only be considered when the pharmacological options have been exploited to the fullest. Patients must be carefully selected. There is an emerging distinction between destructive procedures, which have historically been the only option, and neuromodulatory procedures. This area is fast moving and interested readers will need to keep a watching brief on the literature.

Only patients whose headaches are exclusively unilateral should be considered for destructive surgery, as patients whose attacks have alternated sides are at risk of a contralateral recurrence after surgery. A number of procedures that interrupt either the trigeminal sensory or autonomic (cranial parasympathetic) pathways can be performed, although few are associated with long-lasting results while the adverse effects can be devastating. The procedures that have been reported to show some success include trigeminal sensory rhizotomy via a posterior fossa approach,[196] radiofrequency trigeminal gangliorhizolysis[197] and microvascular decompression of the trigeminal nerve with or without microvascular decompression of the nervus intermedius.[198] Complete trigeminal analgesia may be required for the best results. Complications include diplopia, hyperacusis, jaw deviation, corneal anaesthesia and anaesthesia dolorosa. Aggressive long-term ophthalmic follow-up is essential.

Recently, Leone and colleagues[199] reported the use of posterior hypothalamic neurostimulation, while Dodick[200] has just reported on cutaneous neurostimulation of the occipital nerve, the latter approach being based on a promising report of greater occipital nerve stimulation[201] in other headache forms and the positive effects of greater occipital nerve injection in cluster headache outlined above. Non-destructive modalities demand further examination.

2. Paroxysmal Hemicrania

Paroxysmal hemicrania, like cluster headache, is characterised by strictly unilateral, brief, excruciating headaches that occur in association with cranial autonomic features. Paroxysmal hemicrania differs from cluster headache mainly in the high frequency and shorter duration of individual attacks, although there is a considerable overlap in these characteristics. However, paroxysmal hemicrania responds in a dramatic and absolute fashion to indomethacin, thereby underlining the importance of distinguishing it from cluster headache, which is not responsive to indomethacin.

2.1 Historical Note

Chronic paroxysmal hemicrania was first described by Sjaastad and Dale in 1974, when they reported a case they rather aptly named 'a new treatable headache entity'.[202] They consequently coined the term 'chronic paroxysmal hemicrania' to describe this disorder.[203] The initial cases described were characterised by daily headaches for years without remission. Subsequently, it became apparent that not all patients experienced a chronic, unremitting course; in some patients, discrete headache bouts were separated by prolonged pain-free remissions.[1,204-206] This remitting pattern was named episodic paroxysmal hemicrania.[204]

2.2 Epidemiology

Paroxysmal hemicrania is a rare syndrome, although with increasing awareness, it is being recognised more frequently. The prevalence of paroxysmal hemicrania is not known but the relationship compared with cluster headache is reported to be approximately 1–3%.[207] As cluster headache occurs in approximately 1 in 1000, the estimated prevalence of paroxysmal hemicrania is 1 in 50 000. The disorder has been reported in various parts of the world[208,209] and affects different races.[210]

In contrast to cluster headache, paroxysmal hemicrania predominates in females by a sex ratio of 2.13–2.36 : 1.[207,211] The condition usually begins in

adulthood at the mean age of 34 years and a range of 6–81 years.[211]

2.3 Clinical Features

The attack profile of paroxysmal hemicrania is highly characteristic.[1,207,211,212] The headache is strictly unilateral and without side shift in the majority of patients. However, in four reported cases the headache demonstrated side shift[213-216] and in one patient the pain was bilateral.[217] The maximum pain is most often centred on the ocular, temporal, maxillary and frontal regions; less often, the pain involves the neck, occiput and the retro-orbital regions. The pain may occasionally radiate into the ipsilateral shoulder and arm. The pain is typically excruciating in severity and is described as a 'claw-like', throbbing, aching or boring sensation. The headache usually lasts 2–30 minutes, although it can continue for up to 2 hours. In a retrospective study of 84 patients, the mean duration of attacks was 21 minutes (range 2–120 minutes).[207] In a prospective study of 105 attacks, the mean duration was found to be 13 minutes, with a range of 3–46 minutes.[218] It has an abrupt onset and cessation. Interictal discomfort or pain is present in up to one-third of the patients.[207]

Attacks of paroxysmal hemicrania invariably occur in association with ipsilateral cranial autonomic features. Lacrimation, conjunctival injection, nasal congestion or rhinorrhoea frequently accompany the headache; eyelid oedema, ptosis, miosis and facial sweating are less frequently reported. Interestingly, there is a case description of a patient with otherwise typical paroxysmal hemicrania, including a good indomethacin response, with no autonomic features.[214] Photophobia and nausea may accompany some attacks, although vomiting and phonophobia are rare. There is one case report of a typical migrainous aura occurring in association with paroxysmal hemicrania attacks.[219] During episodes of pain, approximately 50% of patients prefer to sit or lie still, while the other half assume the pacing activity usually seen with cluster headaches.[207]

In paroxysmal hemicrania the attacks occur at a high frequency. The frequency of attacks ranges from 2 to 40 daily. In a retrospective study of 84 patients, the mean attack frequency was 11 per day (range 2–40).[207] In a prospective study of 105 attacks in five patients, the mean attack frequency was 14 per day (range 4–38).[218] The attacks occur regularly throughout the 24-hour period without a preponderance of nocturnal attacks as in cluster headache. However, nocturnal attacks associated with rapid eye movement (REM) phase of sleep have been described.[220]

While the majority of attacks are spontaneous, approximately 10% of attacks may be precipitated mechanically, either by bending or by rotating the head. Attacks may also be provoked by external pressure against the transverse processes of C4-5, C2 root, or the greater occipital nerve. Alcohol ingestion triggers headaches in only 7% of patients.[207]

2.4 Classification

Paroxysmal hemicrania is classified depending on the presence of a remission period. About 20% of patients have episodic paroxysmal hemicrania, which is diagnosed when there are clear remission periods between bouts of attacks that may last from a few weeks to years. The remaining 80% of patients have chronic paroxysmal hemicrania, which is diagnosed when the patients have daily attacks without any clear remission periods. Notably, in paroxysmal hemicrania the chronic form dominates the clinical presentation, in contrast to cluster headache in which the episodic form prevails.

In episodic paroxysmal hemicrania the typical duration of the headache bout ranges from 2 weeks to 4.5 months; remission periods range from 1 to 36 months. In contrast to episodic cluster headache, circannual periodicity does not appear to be a feature of episodic paroxysmal hemicrania, although one case with seasonal onset has been described.[221] In approximately a quarter of the patients with chronic paroxysmal hemicrania, it has evolved from episodic paroxysmal hemicrania, while the remaining three quarters have the chronic form from onset.

The current IHS diagnostic criteria[3] only recognise chronic paroxysmal hemicrania (see table

Table VIII. Diagnostic features of paroxysmal hemicrania modified from the International Headache Society (IHS) Diagnostic criteria for chronic paroxysmal hemicrania[3] with the proposed changes[2]

Paroxysmal hemicrania has two key forms
Episodic: occurs in periods lasting 7 days to 1 year separated by pain free periods lasting 1 month or more[a]
Chronic: attacks occur for more than 1 year without remission or with remissions lasting less than 1 month[a]
Headaches must have each of[b]
Severe unilateral orbital, supraorbital and/or temporal pain lasting 2–45 minutes
Attack frequency about 5 daily for more than half of the time (periods with lower frequency may occur)
Headache associated with at least one of the following signs which have to be present on the pain side
conjunctival injection
lacrimation
nasal congestion
rhinorrhoea
ptosis
eyelid oedema
Absolute effectiveness of indomethacin (≤300 mg/day)[c]

a Proposed changes to IHS diagnostic criteria.[2]

b No reasonable secondary cause.

c The current diagnostic criteria state a dose of 150mg/day but some patients require as much as 300mg/day.

VIII), as episodic paroxysmal hemicrania was not sufficiently validated when these criteria were drawn up. In the forthcoming revision of the IHS classification criteria, chronic and episodic paroxysmal hemicrania will be recognised as subgroups of paroxysmal hemicrania, thus bringing the nomenclature in line with that of cluster headache.

2.5 Secondary Paroxysmal Hemicrania and Associations

Secondary paroxysmal hemicrania is relatively common and can be caused by diverse pathological processes at various sites (see table IX).

Paroxysmal hemicrania has been reported to occur in association with migraine,[232] cluster headache,[209,233-235] trigeminal neuralgia[236-239] and cough headache.[240] Similar to cluster-tic syndrome, the paroxysmal hemicrania-tic syndrome is recognised[241] and requires treatment of both conditions.

2.6 Differential Diagnoses

The differential diagnoses of strictly unilateral, brief, but frequent, headaches are: paroxysmal hemicrania (primary and secondary forms), cluster headache, SUNCT syndrome and trigeminal neuralgia.

There is a considerable overlap in the clinical phenotype of paroxysmal hemicrania and cluster headache: both are strictly unilateral, relatively brief but frequent headaches that occur in association with ipsilateral cranial autonomic features. Mistaking paroxysmal hemicrania for cluster headache is problematic since, generally, treatments for cluster headache are not effective for paroxysmal

Table IX. Causes of secondary paroxysmal hemicrania

Vascular causes
Aneurysms within the circle of Willis[222]
Parietal arteriovenous malformation[223]
Stroke
middle cerebral artery infarct[223]
occipital infarction[224]
Collagen vascular disease[222]
Tumours
Frontal lobe tumour[222]
Gangliocytoma of the sella turcica[225]
Cavernous sinus meningioma[226]
Pituitary microadenoma[227]
Cerebral metastases of parotid epidermoid carcinoma[228]
Pancoast tumour[229]
Miscellanoeus
Maxillary cyst[227]
Intracranial hypertension[230]
Essential thrombocythaemia[231]

hemicrania. Paroxysmal hemicrania differs from cluster headache for its female preponderance, shorter duration of headaches that are more frequent, and the absolute response to indomethacin. The utility of sex of patients, and duration and frequency of the attack, to distinguish paroxysmal hemicrania from cluster headache is limited by the considerable overlap of these characteristics in the two syndromes. It could be advocated that all patients diagnosed with TACs who do not have a contraindication to the use of NSAIDs should have a trial of indomethacin at the start of treatment to detect the indomethacin-sensitive group, at least until a reliable biological marker becomes available. The disadvantage of this approach is that the diagnostic yield will be low (as paroxysmal hemicrania is comparatively rare) and will delay appropriate treatment by 2–3 weeks in patients with cluster headache. The alternative approach is to consider the indomethacin trial only in patients with a high likelihood of having paroxysmal hemicrania; we routinely perform a trial of indomethacin in patients with TAC having more than five attacks daily, or attacks lasting <30 minutes, or both.

2.7 Diagnostic Workup

A good clinical history, a detailed neurological examination and a therapeutic trial of indomethacin are all that are necessary to make a diagnosis of paroxysmal hemicrania. As a relatively high number of symptomatic cases have been reported (see table IX), an MRI scan of the brain should be routinely performed in all patients with paroxysmal hemicrania.

The therapeutic trial of oral indomethacin should be initiated at a dosage of 25mg three times daily. If there is no or a partial response after 10 days, the dose should be increased to 50mg three times daily for 10 days. If the index of suspicion is high then the dose should be further increased to 75mg three times daily for 10 days. Complete resolution of the headache is prompt, usually occurring within 1–2 days of initiating the effective dose, although we have treated a patient who took 10 days to respond to indomethacin (unpublished observation). Injectable indomethacin 50–100mg intramuscularly ('indotest') has been proposed as a diagnostic test for paroxysmal hemicrania.[242] Complete pain relief was reported to occur for 8.2 ± 4.2 hours with intramuscular indomethacin 50mg and 11.1 ± 3.5 hours with intramuscular indomethacin 100mg. The 'indotest' has the advantage that the diagnosis can be rapidly established and, although it needs further validation at this stage, in the absence of a biological marker it is likely to become the test of choice in TACs. In patients who do not respond to indomethacin, the diagnosis should be reconsidered.

Additional investigations are required when secondary paroxysmal hemicrania is suspected. Secondary paroxysmal hemicrania should be considered when the clinical picture is atypical, there are associated neurological signs, the indomethacin dose is escalating or treatment response is poor. A reasonably complete screen of a patient with paroxysmal hemicrania, considering the associated clinical problems reported, would include: (i) an appropriate brain imaging procedure; (ii) blood count (looking for thrombocythaemia); (iii) vasculitis screen (looking for collagen vascular disease); (iv) lumbar puncture (should the pain become bilateral, a lumbar puncture should be performed to look for intracranial hypertension, even in the face of response to indomethacin); and (v) a chest radiograph (looking for a Pancoast tumour).

2.8 Management

The treatment of paroxysmal hemicrania is prophylactic. Indomethacin is the treatment of choice. Complete resolution of the headache is prompt, usually occurring within 1–2 days of initiating the effective dose. The typical maintenance dosage ranges from 25–100 mg/day but dosages up to 300 mg/day are occasionally required. Dosage adjustments may be necessary to address the clinical fluctuations seen in paroxysmal hemicrania. During active headache cycles, skipping or even delaying doses may result in the prompt reoccurrence of the headache. In patients with episodic paroxysmal hemicrania, indomethacin should be given for slightly longer than the typical headache bout and then gradually tapered. In

patients with chronic paroxysmal hemicrania, long-term treatment is usually necessary; however, long lasting remissions have been reported in rare patients following cessation of indomethacin, hence, drug withdrawal should be advised at least once every 6 months. Gastrointestinal adverse effects secondary to indomethacin may be treated with antacids, misoprostol, histamine H_2 receptor antagonists or proton pump inhibitors, and should always be considered for patients who require long-term treatment.

The mechanism behind the absolute responsiveness to indomethacin is unknown. It appears to be independent of the effect of indomethacin on prostaglandin synthesis, since other NSAIDs have little or no effect on paroxysmal hemicrania.

In patients who do not respond to indomethacin, the diagnosis should be reconsidered. Patients who need escalating doses of indomethacin to suppress the symptoms, become refractory to treatment with indomethacin or require a continuous, high dosage of indomethacin may have underlying pathology and need careful diagnostic evaluation for symptomatic causes.

For patients who cannot tolerate indomethacin, the physician faces a difficult challenge. No other drug is consistently effective in paroxysmal hemicrania. Drugs other than indomethacin reported to be partially or completely effective, mainly in isolated case reports, include other NSAIDs (aspirin,[207,243] naproxen,[244] and piroxicam beta-cyclodextrin[245]), the cyclo-oxygenase (COX)-2 inhibitor celecoxib,[246] calcium channel antagonists (verapamil[247,248] and flunarizine[249]), acetazolamide[250] and corticosteroids.[251] We have tried COX-2 inhibitors and verapamil with limited success.

2.9 Natural History and Prognosis

As paroxysmal hemicrania is a relatively recently described syndrome, there is a paucity of literature on its natural history and long-term prognosis. The available evidence suggests that it is a lifelong condition. Patients can expect sustained efficacy of indomethacin treatment without developing tachyphylaxis, although about one-quarter develop gastrointestinal adverse effects.[252] Indomethacin does not seem to alter the condition in the long-term, although a significant proportion of patients can decrease the dose of indomethacin required to maintain a pain-free state.

3. Short Lasting Unilateral Neuralgiform Headache Attacks with Conjunctival Injection and Tearing (SUNCT)

SUNCT syndrome, like the other TACs, manifests as a unilateral headache that occurs in association with cranial autonomic features. The features that distinguish it from the other TACs are: very brief duration of attacks that can occur very frequently and the presence of prominent conjunctival injection and lacrimation, both of which are present in the vast majority of patients. For the reason that some patients with clinically the same problem, but in whom one of conjunctival injection or tearing are absent, we feel the syndrome should be renamed SUNA: Short-lasting Unilateral Neuralgiform headache attacks with cranial Autonomic features.

3.1 Historical Note

SUNCT syndrome was only described relatively recently; the entity was first described in 1978[253] and more fully characterised in 1989.[254]

3.2 Epidemiology

The prevalence or incidence of SUNCT syndrome are not known, although the extremely low number of reported cases suggests that it is a very rare syndrome. We found only 53 complete case descriptions in the English language literature.[1,255-277] The disorder has a male predominance (36 males, 17 females) with a sex ratio of 2.1 : 1. The typical age of onset is between 40 and 70 years, although it ranges from 10 to 77 years (mean 52 years).

3.3 Clinical Features

The pain is usually maximal in the ophthalmic distribution of the trigeminal nerve, especially the orbital or periorbital regions, forehead and temple, although it may radiate to the other ipsilateral trigeminal divisions. Attacks are typically unilateral; however, in three patients the pain was simultaneously experienced on the opposite side.[255] The severity of pain is generally moderate to severe. The pain is usually described as stabbing, burning, pricking or electric shock-like in character. The individual attacks are very brief, lasting between 5–250 seconds (mean duration 49 seconds),[278] although attacks lasting up to 2 hours each have been described.[258,276,279] The paroxysms begin abruptly, reaching the maximum intensity within 2–3 seconds; the pain is maintained at the maximum intensity before abating rapidly.[255] Most patients are completely pain-free between attacks, although some report a persistent dull interictal discomfort.[279]

The temporal pattern is quite variable, with the symptomatic periods alternating with remissions in an erratic manner. Symptomatic periods generally last from a few days to several months, and occur once or twice annually. Remissions typically last a few months, although they can range from 1 week to 7 years. Symptomatic periods appear to increase in frequency and duration over time.[255]

The attack frequency during the symptomatic phase varies immensely between patients and within an individual patient. Attacks may be as infrequent as once a day or less or more frequent than 30 attacks an hour. Rarely, patients report attacks that recur in a repetitive and overlapping fashion for 1–3 hours at a time.[280] Most SUNCT attacks occur during the daytime, tending to show a bimodal distribution with morning and afternoon/evening predominance. Nocturnal attacks are seldom reported; objective assessment of the timing of the attacks demonstrated that only 1.2% occurred at night.[278]

Acute headache episodes in SUNCT syndrome are accompanied by a variety of associated symptoms. The attacks are virtually always accompanied by both ipsilateral conjunctival injection and lacrimation. Ipsilateral nasal congestion, rhinorrhoea, eyelid oedema, ptosis, miosis and facial redness or sweating are less commonly reported. These cranial autonomic symptoms, particularly conjunctival injection and lacrimation, are typically very prominent in SUNCT syndrome. The associated conjunctival injection and tearing usually begin 1–2 seconds after onset of the pain and may outlast the pain by a few seconds. Rhinorrhoea, when present, is delayed, occurring relatively late in the course of the headache. Nausea, vomiting, photophobia and phonophobia are not normally associated with SUNCT syndrome. Unlike in cluster headache, restlessness is not a feature of SUNCT syndrome.[255]

The majority of patients can precipitate attacks by touching certain trigger zones within trigeminal innervated distribution and, occasionally, even from an extra-trigeminal territory. Precipitants include touching the face or scalp, washing, shaving, eating, chewing, brushing teeth, talking and coughing.[255] Neck movements can also precipitate attacks, although some patients can lessen or abort attacks by continuously rotating their neck.[254,255] Unlike in trigeminal neuralgia, most patients have no refractory period.

Suggested clinical criteria for the diagnosis of SUNCT syndrome are listed in table X.

3.4 Secondary SUNCT

Secondary SUNCT has been reported in seven patients, all of who have had posterior fossa abnor-

Table X. Diagnostic criteria for short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT)

Headaches must have each of[a]
Attacks of unilateral moderately severe orbital or temporal stabbing or throbbing pain lasting 5–250 seconds
Attack frequency 3–100/day
Pain is associated with at least one of the following signs or symptoms on the affected side, with conjunctival injection being most often present and very prominent
conjunctival injection
lacrimation
nasal congestion
rhinorrhoea
ptosis
eyelid oedema

a No reasonable secondary cause.

malities. The secondary causes include homolateral cerebellopontine angle arteriovenous malformations in two patients,[281,282] a brainstem cavernous hemangioma,[256] a posterior fossa lesion in a patient with HIV/AIDS,[1] severe basilar impression causing pontomedullary compression in a patient with osteogenesis imperfecta,[270] craniosynostosis resulting in a foreshortened posterior fossa[266] and ischemic brainstem infarction.[267] These posterior fossa abnormalities emphasise the absolute need for a cranial MRI in any suspected case of SUNCT. Our experience[283] and other reported cases[284,285] suggest that a SUNCT-like picture may be seen with pituitary adenomas and that this is not related to tumour size.[286]

3.5 Differential Diagnoses

The differential diagnoses of very brief headaches include: SUNCT (primary and secondary forms), trigeminal neuralgia, primary stabbing headache and paroxysmal hemicrania.

Differentiating SUNCT from trigeminal neuralgia can be challenging in some patients, as there is a considerable overlap in the clinical phenotypes of the two syndromes. Both headaches are short lasting, can have a high frequency of attacks and display clustering of attacks. Both are principally unilateral headaches and the trigger zones behave similarly. The usual onset is during middle or old age in both. However, there are a number of striking differences between these two syndromes (see table XI), awareness of which can aid in their differentiation.[287,288]

Primary stabbing headache (also known as idiopathic stabbing headache) refers to brief, sharp or jabbing pain in the head that occurs either as a single episode or in brief repeated volleys. The pain is usually over the ophthalmic trigeminal distribution, while the face is generally spared. The pain usually lasts a fraction of a second but can persist for up to 1 minute, thereby overlapping with the phenotype of SUNCT, and recurs at irregular intervals (hours to days). These headaches are generally easily distinguishable clinically as they differ in several respects: in primary stabbing headache there is: (i) a female preponderance; (ii) the site and radiation of pain often varies between attacks; (iii) the majority of the attacks tend to be spontaneous; (iv) cranial autonomic features are absent; and (v) the attacks commonly subside with the administration of indomethacin.[289,290]

SUNCT syndrome also has to be differentiated from short-lasting paroxysmal hemicrania. Paroxysmal hemicrania prevails in females; the attacks have a uniform distribution through day and night; the triggers differ from those in SUNCT; and the attacks are exquisitely responsive to indomethacin. If there is any diagnostic uncertainty then a trial of indomethacin is warranted.

3.6 Treatment

Until recently, SUNCT was thought to be highly refractory to treatment.[291] Several categories of drugs used in other headache syndromes i.e. NSAIDs (including indomethacin), paracetamol (acetaminophen), 5-HT receptor agonists (triptans, ergotamine and DHE), β-blockers, tricyclic antidepressants, calcium channel antagonists (verapamil and nifedipine), methysergide, lithium, prednisone (or prednisolone), phenytoin, baclofen and intravenous lidocaine have proved to be ineffectual.[291] Our experience with intravenous lidocaine is very different and we have found it very effective (Matharu and Goadsby, unpublished data), although we have now tested more than the two patients reported by Pareja and colleagues.[291] Partial im-

Table XI. Differentiating features of typical SUNCT and trigeminal neuralgia

Feature	SUNCT	Trigeminal neuralgia
Gender ratio (male : female)	2.1 : 1	1 : 2
Site of pain	V1	V2/3
Severity of pain	Moderate to severe	Very severe
Duration (seconds)	5–250	<5
Autonomic features	Prominent	Sparse or none
Refractory period	Absent	Present
Response to carbamazepine	Partial	Complete

SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; **V1** = ophthalmic trigeminal distribution; **V2/3** = mandibular and maxillary trigeminal distribution.

provement with carbamazepine has been observed in several patients.[258,261,276,291,292]

Recently, lamotrigine has been reported to be highly efficacious in a number of patients.[264,272,293] Lamotrigine, given in an open-label manner at 100–300 mg/day, induced a complete remission in seven patients and produced about an 80% improvement in the other two patients. Although the ultimate confirmation of the utility of lamotrigine in the treatment of this debilitating syndrome should come from a randomised double-blind, placebo-controlled clinical trial, for now, it is the treatment of choice.

There are a number of case report of patients with SUNCT who responded completely to gabapentin,[262,277,294] typically 900–2700 mg/day. We have recently reported a patient who responded completely to topiramate 50 mg/day.[276] These observations clearly need to be confirmed in other patients. Nonetheless, given the debilitating nature of this headache, gabapentin and topiramate are reasonable second line agents in patients who fail a trial of lamotrigine.

Several surgical approaches have been tried in SUNCT syndrome. Anaesthetic blockades of pericranial nerves have been reported to be ineffective.[291] There are six case reports of apparently successful treatment of SUNCT syndrome with surgical procedures. Two patients were treated with the Jannetta procedure[295,296] and one with percutaneous trigeminal ganglion compression. Three patients were treated with retrogasserian glycerol rhizolysis, two of whom were treated twice. All five treatments provided complete pain relief, although the duration of the benefit ranged from 2 to 4.5 years. One of these patients went on to have a trigeminal nerve balloon compression with a good result.[275] In addition, there is one report of a partial response with local opioid blockade of the superior cervical ganglion.[268] However, follow-up in some of these patients was limited to less than 18 months, which makes it difficult to assess the actual effectiveness of the procedures given the episodic nature of the syndrome.

Black and Dodick[274] have reported two patients with SUNCT refractory to various surgical procedures. The first patient underwent a glycerol rhizotomy, gammaknife radiosurgery and microvascular decompression of the trigeminal nerve, while the second patient underwent gammaknife radiosurgery of the trigeminal root exit zone and two microvascular decompressions of the trigeminal nerve. Neither patient benefited from these procedures. In addition, the first patient experienced anaesthesia dolorosa and the second patient unilateral deafness, chronic vertigo and dysequilibrium as a result of surgery. Hannerz and Linderoth[275] made a brief reference to a patient who had not benefited from trigeminal vascular decompression and two gammaknife radiosurgeries of the trigeminal root. We have seen two patients who had failed to demonstrate a persistent response following trigeminal thermocoagulation and microvascular decompression (unpublished observations).

Given the uncertain efficacy of trigeminal procedures together with the potential for complications, surgery should only be considered as a last resort and only when the pharmacological options have been exploited to the fullest.

3.7 Natural History

The natural history of SUNCT syndrome is poorly understood. In a series of 21 patients, the average duration of symptoms was 11.8 years. In ten of these patients the duration of SUNCT exceeded 10 years. The longest reported duration of SUNCT is 48 years.[255] It appears to be a lifelong disorder once it starts, although more prospective data is needed. The syndrome itself is not fatal and does not cause any long-term neurological sequelae.

4. Hemicrania Continua

Hemicrania continua, like paroxysmal hemicrania, is an indomethacin-responsive headache. Unlike the other TACs, which are intermittent short-lasting headaches, hemicrania continua is characterised by a continuous, unilateral headache that varies in intensity, waxing and waning without disappearing completely.

4.1 Historical Note

Hemicrania continua was probably first described by Medina and Diamond in 1981.[297] Sjaastad and Spierings[298] coined the term 'hemicrania continua' in 1984 when they described two further cases. Since then over 130 cases have been described in the literature.

4.2 Epidemiology

The incidence and prevalence of hemicrania continua is not known. It was thought to be a very rare syndrome; however, headache clinics which have systematically sought this entity have rapidly identified significant number of patients, thereby suggesting that the condition is underdiagnosed and may be more common than has been appreciated.[299,300]

The disorder has a female preponderance with a sex ratio of 2.4 **:** 1. The condition usually begins in adulthood, although the range of age of onset is 5–67 years (mean 28 years).[299]

4.3 Clinical Features

Hemicrania continua is a unilateral, continuous headache; in the vast majority of patients the pain is exclusively unilateral without sideshift, although rare bilateral cases[301-303] and a patient with unilateral, side-alternating attacks[304] have been described. The forehead, temporal, orbit and occiput are the most frequent sites of pain, although any part of the head or neck can be affected.[305] Typically, the pain is mild to moderate in intensity. The quality of pain is described as dull, aching or pressing. It is not usually associated with photophobia, phonophobia, nausea, vomiting or cranial autonomic symptoms.[299,305,306]

In the vast majority (74–100%) of patients, exacerbations of severe pain are superimposed on the continuous baseline pain. These exacerbations can last from 20 minutes to several days. In a third of patients they occur at night and can result in a mistaken diagnosis of cluster headache or hypnic headache. The exacerbations may occur in association with cranial autonomic symptoms and migrainous features. Autonomic symptoms are present in 63–74% of patients with hemicrania continua but are not as prominent as in patients with cluster headache or paroxysmal hemicrania. The most common autonomic symptoms are lacrimation and conjunctival injection. Migrainous features (photophobia, phonophobia, nausea and vomiting) are very common during exacerbations, with 71% of patients satisfying IHS classification for migraine. Recently, four patients have been described in whom a typical migrainous visual aura occurred in association with the exacerbation of hemicrania continua.[307] There is a general paucity of precipitating factors: neck movements do not trigger exacerbations, although occipital tenderness is present in 68 percent of patients (ipsilateral 44%, bilateral 24%).[299,306] In 26–41% of patients, primary stabbing headaches occur, predominantly during the exacerbations.[299]

4.4 Classification

Although hemicrania continua is continuous or unremitting in the majority of patients, some have an episodic or remitting form with distinct headache phases separated by pain-free remissions. Like cluster headache and paroxysmal hemicrania, hemicrania continua can be classified into an episodic and chronic form depending on the temporal profile.[306] Hemicrania continua is chronic from onset in 53%, chronic evolved from episodic in 35% and episodic from onset in 12% of patients.[299] There is one case report of a patient who became episodic following a chronic onset.[308]

4.5 Secondary Hemicrania Continua and Associations

Although there are no reports of secondary hemicrania continua, a C7 root irritation as a result of a disc herniation has been noted to aggravate the condition.[226] A patient with HIV developed hemicrania continua, although whether this was causal is unclear.[309] A report of a patient with a mesenchymal tumour in the sphenoid bone has also been published in which the response to indomethacin faded after 2 months.[310] This suggests that escalating doses or loss of efficacy of indomethacin should

be treated with suspicion and the patient re-evaluated. Eight cases of post-traumatic hemicrania continua have been reported, although the temporal relationship of the trauma to the onset of hemicrania continua is very variable.[311]

In 26–41% of patients, primary stabbing headaches occur predominantly during the exacerbations.[299]

4.6 Differential Diagnoses

The differential diagnoses of long-lasting unilateral headache include: (i) hemicrania continua (primary and secondary forms); (ii) unilateral chronic migraine or new daily persistent headache (NDPH); (iii) cervicogenic headache; and (iv) the other TACs occurring in association with a constant, unilateral interictal dull ache, particularly paroxysmal hemicrania.

Hemicrania continua can be readily differentiated from chronic migraine and NDPH by the indomethacin responsiveness.[312] In addition, it is worth noting that patients with hemicrania continua can develop a bilateral headache typical of rebound headaches if they overuse analgesics: there are reports of three patients with what appeared to be chronic migraine with analgesia overuse, in whom on withdrawing analgesics hemicrania continua was uncovered. All three patients responded to treatment with indomethacin.[313]

Cervicogenic headache is caused by disease or dysfunction of structures in the neck. It is characterised by: (i) pain localised to the neck and occipital region, although may radiate anteriorly; (ii) precipitation or aggravation by neck movements or a sustained neck posture; and (iii) local neck signs such as limitation of movement or abnormal tenderness. Hemicrania continua can be readily differentiated from cervicogenic headache on the basis of several factors. In hemicrania continua the pain is usually centred on the ophthalmic trigeminal distribution (rather than the neck and occiput as in cervicogenic headache), there is a paucity of mechanical precipitation of attacks and the response to indomethacin is absolute.[314]

Some patients with the other TACs report a persistent dull background ache in the territory of their usual attack. This may be particularly problematic in differentiating hemicrania continua and chronic paroxysmal hemicrania, when the latter has inter-ictal pain. Some clinical features can help. First, interictal pain in chronic paroxysmal hemicrania is usually described as mild only, whereas background pain in hemicrania continua is often moderate (although it can be mild). Secondly, exacerbations in chronic paroxysmal hemicrania are short lasting (2 minutes–1 hour), whereas those in hemicrania continua are longer lasting, often lasting several hours. Thirdly, the severity of pain during exacerbations is excruciating in chronic paroxysmal hemicrania, whereas in hemicrania continua often moderate or severe. A biological marker will be required to gain insight into how best to differentiate these syndromes.

4.7 Investigations

The diagnosis is made on the basis of clinical history, neurological examination and a therapeutic trial of indomethacin. An MRI scan of the brain is a reasonable screening investigation to exclude secondary causes.

All patients with unilateral chronic daily headache in whom secondary causes have been excluded should have a trial of indomethacin. The trial of oral indomethacin is performed using the protocol already described for paroxysmal hemicrania. The response to indomethacin treatment is usually rapid, with complete resolution of the headache within 1–2 days of initiating the effective dose. ‘Indotest’, that is, injectable indomethacin 50–100mg intramuscularly, has been proposed as a diagnostic test for hemicrania continua.[242] Complete pain relief was reported to occur within 2 hours. The ‘indotest’ has the advantage that the diagnosis can be rapidly established and when performed at the higher dose (100mg) is likely to avoid the problem of an inadequate oral indomethacin trial. Although not widely available as yet, it is likely to become the test of choice in unilateral primary chronic daily headache.

4.8 Treatment

The treatment of hemicrania continua is prophylactic. As with paroxysmal hemicrania, hemicrania continua has a prompt and enduring response to indomethacin. The reported effective dose of indomethacin ranges from 25–300 mg/day.[299,306] Dosage adjustments may be necessary to address clinical fluctuations. Skipping or delaying doses may result in the recurrence of the headache. Concurrent treatment with gastric mucosa protective agents should be considered for patients requiring long-term treatment.

No other drug is consistently effective in hemicrania continua. Other NSAIDs are generally of little or no benefit. Other drugs reported to be partially or completely effective, usually in isolated cases, include ibuprofen,[306,315] piroxicam betadex,[245] naproxen,[305] aspirin,[316] the COX-2 inhibitor rofecoxib,[317] and paracetamol with caffeine.[305]

Six patients have been described who had the clinical phenotype of hemicrania continua but did not respond to indomethacin.[318,319] This raises the question whether there is a subset of patients with the underlying biology and clinical phenotype of hemicrania continua who do not respond to indomethacin. If the mode of action of indomethacin involves interrupting the central pathogenetic mechanism of hemicrania continua, then it is likely that all patients will respond to indomethacin and the indomethacin-resistant patients do not represent true hemicrania continua. However, until the underlying pathophysiology of hemicrania continua and the mode of action of indomethacin are better understood, this issue will remain unresolved. Diagnostic criteria have been proposed that accommodate both indomethacin-responsive and indomethacin-resistant patients who fit the clinical phenotype (see table XII),[1] and these criteria seem useful in clinical practice.[320] However, the main use of these criteria is in research; for clinical practice, it is prudent to only diagnose hemicrania continua in patients who are responsive to indomethacin.[321]

Table XII. Diagnostic criteria for hemicrania continua

Headaches must have each of[a]
Headache present for at least 1 month
Unilateral headache
Pain has all of the following present
continuous but fluctuating
moderate severity, at least some of the time
lack of precipitating mechanisms
Absolute response to indomethacin, or one of the following autonomic features in association with exacerbation of pain
conjunctival injection
lacrimation
nasal congestion
rhinorrhoea
ptosis
eyelid oedema

a No reasonable secondary cause.

4.9 Natural History and Prognosis

As hemicrania continua is a relatively recently described entity, it's natural history is still being determined. It appears to be a chronic condition in most patients, although several cases have been reported in whom indomethacin could be discontinued and the patients remained pain-free.[306,316] Patients should be advised to discontinue the indomethacin at least once every 6 months to ensure that they are still symptomatic and the dose titrated to the minimum effective.

As with paroxysmal hemicrania, patients with hemicrania continua can expect an enduring response to indomethacin without developing tachyphylaxis, although between a quarter to half develop gastrointestinal adverse effects.[252,306] Indomethacin does not seem to alter the condition in the long-term, although a significant proportion of patients can decrease the dose of indomethacin required to maintain a pain-free state.[252]

5. Pathophysiology of TACs

Any pathophysiological construct for TACs must account for the two major clinical features characteristic of the various conditions that comprise this group: trigeminal distribution pain and ipsilateral autonomic features.[11] The pain-producing innervation of the cranium projects through branches of the

trigeminal and upper cervical nerves to the trigeminocervical complex from whence nociceptive pathways project to higher centres. This implies an integral role for the ipsilateral trigeminal nociceptive pathways in TACs. The ipsilateral autonomic features suggest cranial parasympathetic activation (lacrimation, rhinorrhoea, nasal congestion and eyelid oedema) and sympathetic hypofunction (ptosis and miosis). Goadsby and Lipton have suggested that the pathophysiology of the TACs revolves around the trigeminal-autonomic reflex.[1] There is considerable experimental animal literature to document that stimulation of trigeminal efferents can result in cranial autonomic outflow, the trigeminal-autonomic reflex.[322] In fact, some degree of cranial autonomic symptomatology is a normal physiological response to cranial nociceptive input[323] and patients with other headache syndromes may report these symptoms.[324] The distinction between the TACs and other headache syndromes is the degree of cranial autonomic activation.[288]

The cranial autonomic symptoms may be prominent in the TACs as a result of a central disinhibition of the trigeminal-autonomic reflex.[288] Supporting evidence is emerging from functional imaging studies: a positron emission tomography study in cluster headache[174] and a functional MRI study in SUNCT syndrome[260] have both demonstrated ipsilateral hypothalamic activation. Hypothalamic activation is specific to these syndromes and is not seen in migraine[325,326] or experimental ophthalmic trigeminal distribution head pain.[327] There are direct hypothalamic-trigeminal connections[328] and the hypothalamus is known to have a modulatory role on the nociceptive and autonomic pathways. Hence, cluster headache and SUNCT syndrome are probably due to an abnormality in the hypothalamus with subsequent trigeminovascular and cranial autonomic activation.

There are several issues that remain unresolved in the understanding of the pathophysiology of the TACs. Further studies need to seek the anatomical or functional basis of the variations in patterns of expression of pain and autonomic symptoms in the different TACs. As in cluster headache and SUNCT, the central locus of abnormality in paroxysmal hemicrania and hemicrania continua needs to be identified. The nature of the hypothalamic abnormality in cluster headache and SUNCT needs to be elucidated. Finally, the mechanism of action of indomethacin needs to be unravelled. Advances in the pathophysiological understanding of these conditions is likely to lead to better treatments for these devastatingly painful syndromes.

6. Conclusion

Cluster headache, paroxysmal hemicrania, SUNCT syndrome and hemicrania continua are fairly stereotyped headache syndromes that can be recognised and differentiated from other headache syndromes with relative ease. Functional imaging studies have started to unravel the underlying basis of these conditions and point to the fundamental involvement of the hypothalamus in cluster headache and SUNCT syndrome. The ultimate goal of this research is to improve the treatment of the patients. While we optimistically await the arrival of more efficacious and better drugs, it is worth bearing in mind that there are already several effective abortive and preventive treatments for cluster headache and, recently, there have been important advances in the therapeutics of SUNCT syndrome. Paroxysmal hemicrania and hemicrania continua are rapidly and exquisitely responsive to indomethacin. The potential for rapid and effective pain relief underlines the importance of rapid diagnosis and appropriate treatment of these of these highly painful syndromes.

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