Cluster Headache: Diagnosis and Treatment

Rashmi Halker, M.D.,[1] Bert Vargas, M.D.,[1] and David W. Dodick, M.D.[1]

ABSTRACT

Cluster headache is a rare yet exquisitely painful primary headache disorder occurring in either episodic or chronic patterns. The unique feature of cluster headache is the distinctive circadian and circannual periodicity in the episodic forms. The attacks are stereotypic—they are of extreme intensity and short duration, occur unilaterally, and are associated with robust signs and symptoms of autonomic dysfunction. Although the pathophysiology of cluster headache remains to be fully understood, there have been a number of recent seminal observations. To exclude structural mimics, patients presenting with symptoms suggestive of cluster headache warrant at least a brain magnetic resonance imaging (MRI) scan in their work-up. The medical treatment of cluster headache includes acute, transitional, and maintenance prophylaxis. Agents used for acute therapy include inhalation of oxygen, triptans, such as sumatriptan, and dihydroergotamine. Transitional prophylaxis refers to the short-term use of fast-acting agents. This typically involves either corticosteroids or an occipital nerve block. The mainstay of prophylactic therapy is verapamil. Yet, other medications, including lithium, divalproex sodium, topiramate, methysergide, gabapentin, and even indomethacin, may be useful when the headache fails to respond to verapamil. For medically refractory patients, surgical interventions, occipital nerve stimulation, and deep brain stimulation remain an option. As the sophistication of functional neuroimaging increases, better insight into the pathophysiological mechanisms that underlie cluster headache is expected.

KEYWORDS: Cluster headache, prophylaxis, occipital nerve stimulation, deep brain stimulation

CLINICAL FEATURES

Cluster headache has been portrayed as being the most painful of the primary headache disorders, with some women sufferers comparing the pain of an attack as worse than childbirth, and other individuals contemplating or even attempting suicide during an attack as a way to end the pain.

Several clinical features can help characterize cluster headache. The pain usually comes without warning, is extremely severe, unilateral, often maximal around and behind the orbit, and commonly described as piercing, boring, or stabbing. The headache may begin or become referred to the temporal, lower facial, or occipital region; it peaks within 3 to 5 minutes and lasts 60 to 90 minutes on average, with a range of 15 to 180 minutes (Table 1).

Almost without exception, attacks are strictly unilateral in any cluster period and may remain unilateral on the same side throughout the individual's history. Less frequently, the pain may occur on the opposite side of the head and face in a subsequent cluster, and even less frequently, attacks will switch sides from one attack to another. Each attack is associated with ipsilateral cranial autonomic symptoms, which include lacrimation, rhinorrhea, conjunctival injection, ptosis, miosis, facial, or periorbital edema. In some patients, these autonomic

[1]Department of Neurology, Mayo Clinic Arizona, Phoenix, Arizona.
Address for correspondence and reprint requests: David W. Dodick, M.D., Department of Neurology, Mayo Clinic Arizona, 5777 East Mayo Blvd., Phoenix, AZ 85054 (e-mail: dodick.david@mayo. edu).
Headache; Guest Editor, Jerry W. Swanson, M.D., F.A.C.P.

Semin Neurol 2010;30:175–185.
DOI: http://dx.doi.org/10.1055/s-0030-1249226.
ISSN 0271-8235.

Table 1 International Headache Society Criteria for Cluster Headache

Cluster headache

1. At least five attacks fulfilling Criteria 2 and 4
2. Severe, unilateral, orbital, supraorbital and/or temporal pain lasting 15–180 minutes untreated
3. Headache is associated with at least one of the following signs that have to be present on the pain side:
   - Conjunctival injection
   - Miosis
   - Ptosis
   - Eyelid edema
   - Forehead and facial sweating
   - Lacrimation
   - Nasal congestion
   - Rhinorrhea
4. Frequency of attacks: one every other day to eight per day

Episodic cluster headache

1. Occurs in periods lasting 7 days to 1 year separated by pain-free periods lasting 14 days or more; cluster periods usually last between 2 weeks and 3 months
2. At least two cluster periods lasting from 7 days to 1 year (untreated), separated by remissions of at least 14 days

Chronic cluster headache

1. Attacks occur for more than 1 year without remission, or remissions last less than 14 days
2. Absence of remission phases for 1 year or more, or remissions last less than 14 days

symptoms may occur on both sides, but remain maximal on the side of the pain. Unlike migraine, where activity aggravates the pain, restlessness and motor agitation is highly characteristic and is reported in over 90% of patients with cluster headache.

Until recently, cluster headache was not considered to be associated with aura symptoms as seen in migraine, but a group of six cluster headache patients who had stereotyped aura (visual aura in five of six patients) preceding individual cluster attacks was recently reported. Other symptoms classically associated with migraine—photophobia, phonophobia, and nausea—occur in a significant number of patients with cluster headache. Photophobia and phonophobia, which are ipsilateral to the pain, occur in up to 50% of individuals with cluster and other trigeminal autonomic cephalalgias (TACs), compared with less than 5% of migraine sufferers.[1]

PERIODICITY

In its most common form, episodic cluster headache occurs at least once every 24 hours for weeks at a time. A common pattern, especially in the first few years of cluster headache, is for cluster periods to occur seasonally: for example, every spring or every fall for a few years. This periodicity generally becomes less evident after a few years and periods of cluster activity become much less predictable, occurring at almost any time of the year. Cluster period frequency is associated with the number of hours of daylight; higher within 2 weeks following the summer and winter solstices, and lowest within 2 weeks of the onset and offset of daylight saving time.

It is an indication that an individual may be switching from the episodic form of the disease to the chronic form when exacerbations lengthen, remissions shorten, or more cluster cycles occur than usual. Once chronic cluster headache has developed, whether de novo or by transformation from the episodic form, it tends to persist for years, even into old age, although long-term follow-up has shown that up to 50% of affected individuals eventually revert to or switch to an episodic form.

During a cluster period or in the chronic phase, individual attacks of headache occur daily or almost daily. When only one attack occurs in 24 hours, it is not uncommon for each attack to occur at the same time each day or each night for days or weeks on end. Unlike migraine or trigeminal neuralgia, nocturnal attacks of cluster headache are more frequent than daytime attacks. Onset of the first attack ~90 minutes after falling asleep may be related to the onset of rapid eye movement (REM) sleep.

Once a cluster period begins, discrete headaches can, in many patients, be triggered or precipitated by ingestion of alcohol and by other vasodilators, notably nitroglycerin and histamine. During remission periods, alcohol rarely precipitates an attack; as a result, most sufferers will avoid alcohol as soon as a drink triggers an attack and will remain abstinent until the cluster is over. Cigarette and heavy alcohol use are relatively common among patients with cluster headache, with up to 85% of cluster patients admitting to smoking and alcohol

consumption being higher in cluster patients than in controls.

The individual attack, which lasts an average of 60 to 90 minutes, is called a cluster headache or cluster attack. The period over which attacks recur is referred to as the cluster period. When attacks cease, the individual is in remission. Typically, a cluster period lasts 6 to 12 weeks, whereas remissions last for an average of 12 months. Episodic cluster headache implies that substantial remissions occur; fortunately, this is true for 85% of cluster patients. Chronic cluster headache, which occurs in ~15% of patients, evolves from the episodic form in ~5%, whereas ~10% have a primary chronic pattern from the start.

DIFFERENTIAL DIAGNOSIS

Cluster headache is the prototype of the group of primary headache disorders referred to as TACs. The TACs are so-named because of the pain distribution (first division of trigeminal nerve) and accompanying ipsilateral cranial autonomic symptoms (i.e., lacrimation, conjunctival injection, rhinorrhea). The other TACs include episodic and chronic paroxysmal hemicrania and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features (SUNCT/SUNA).

As a group, the TACs are set apart by discrete short-lasting episodic attacks of severe, unilateral, orbital-temporal pain associated with profound ipsilateral autonomic features. These syndromes may be associated with nocturnal attacks and can be triggered by alcohol. SUNCT syndrome appears to be the only other headache disorder besides cluster headache which predominates in men. Compared with cluster headache, these disorders differ mainly in the higher frequency and shorter duration of individual attacks with an almost inverse relationship across these disorders—as attack frequency increases, attack duration tends to decrease. Making the distinction between cluster headache and other TACs is important because of the differential response to therapy. The paroxysmal hemicranias often respond in a dramatic fashion to indomethacin, whereas patients with SUNCT syndrome derive no benefit from indomethacin or drugs typically used to treat cluster headache (Table 2).

Migraine may present with recurrent unilateral headache, occasionally with ipsilateral autonomic symptoms, particularly during severe attacks. However, the periodicity of cluster headache is often very stereotyped for a given patient and the attacks of cluster headache are short-lived (45 to 90 minutes) compared with migraine (4 to 72 hours). Furthermore, cluster attacks are almost always unilateral, frequently nocturnal, can occur several times per day, and usually are not associated with aura, nausea, or vomiting.

Temporal arteritis pain is usually persistent but may wax and wane, and there are often systemic symptoms (fever, polymyalgia, weight loss) associated with this disorder. Trigeminal neuralgia is characterized by paroxysmal shock-like electric jabs of unilateral pain, most commonly limited to the distribution of the second and/or third divisions of the trigeminal nerve. The pain can be triggered by stimulation of specific areas of facial skin or oral mucosa.

Other disorders that can mimic cluster headache in the appropriate context are dissection of the cervicocephalic cerebral blood vessels (carotid or vertebral), sinusitis, glaucoma, intracranial aneurysms, central nervous system (CNS) demyelination, tumors or arteriovenous malformations, and even cervical cord lesions (meningioma) or infarction. In many of these instances, the history and examination disclose features that are worrisome for a secondary cause, the history lacks the typical stereotyped periodicity of attack and remission phases, or the response to conventional medications is lacking.

DIAGNOSTIC EVALUATION

In an effort to identify features that would warrant brain imaging in patients who present with a cluster headache or other TAC-like syndrome, a recent case series documented 56 patients who had a secondary cause. Many of these individuals had a typical history, clinical picture, and response to standard treatment, but were found to have a secondary cause on neuroimaging.[2] These results make the argument that all patients who present with a presumed diagnosis of cluster headache or other TAC warrant at least a brain magnetic resonance imaging (MRI) scan, and perhaps additional imaging of the vasculature, sellar, and parasellar region, depending on the degree of suspicion.

Baseline electrocardiogram and serum chemistry are indicated before initiating treatment, which often includes the use of corticosteroids, triptans, and verapa-

Table 2 Cluster Headache: Comparison with Other Trigeminal-Autonomic Cephalgias

Feature	Cluster	CPH	SUNCT
Attack duration mean (mins)	60 minutes	15 minutes	60 seconds
Attack frequency	1–8/day	1–40/day	1/day–30/hour
Treatment of 1st choice	Verapamil	Indomethacin	Lamotrigine

CPH, chronic primary headache; SUNCT, short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing.

mil. Overnight polysomnography may be indicated if features of obstructive sleep apnea (OSA) are present, as OSA is a frequent comorbid condition.

ACUTE (SYMPTOMATIC) THERAPY

Due to the sudden onset and short time to peak intensity, acute attacks of cluster headache require rapidly acting symptomatic treatment. Oxygen inhalation, sumatriptan, dihydroergotamine, zolmitriptan, and local anesthetics provide the fastest, most effective, consistent pain relief from cluster headache attacks.

Oxygen

Oxygen inhalation has been the standard of care for the symptomatic relief of cluster headache since it was found to be an effective therapy in the 1950s. If delivered at attack onset via a non-rebreather facial mask at a flow rate of 7 to 15 liters per minute for 15 minutes, ~70% of patients will obtain relief within 15 minutes. In some patients, oxygen is most effective if taken when the pain is at maximal intensity; in others, the attack may only be delayed for minutes to hours rather than completely aborted. Oxygen therapy has obvious practical limitations in that treatment is not always accessible, and some find the portable cylinders to be difficult to use at work or outside the home.

Recently, the effects of oxygen on the trigeminal nerve and on autonomic responses were studied in the rat model using dural electrical stimulation and 100% oxygen at 1 L/min for 15 minutes.[3] Meningeal vasodilation and activation of the trigeminocervical complex did not change with 100% oxygen; stimulation of the superior salivatory nucleus caused firing of neurons in the trigeminocervical complex and led to changes in blood flow in the lacrimal duct and sac. These results are the first to propose that oxygen may work directly on the parasympathetic facial/greater petrosal nerve pathway to abort a cluster attack, rather than on trigeminal afferents to dural vasculature or within the trigeminal nucleus caudalis.

Sumatriptan

Subcutaneous sumatriptan is the most effective self-administered medication for the symptomatic relief of cluster headache. In a placebo-controlled study, 6 mg of sumatriptan delivered subcutaneously was significantly effective at aborting a cluster attack, with 74% of patients having complete relief by 15 minutes compared with 26% of patients treated with placebo.[4] In long-term open label studies, sumatriptan was effective in 76 to 100% of all attacks within 15 minutes with no evidence of tachyphylaxis or rebound headache even after repetitive daily use for several months.[5,6] This agent is available in a 4 mg dose and might be considered for patients who have more than two cluster headaches per 24 hours to allow for a maximum of three doses per 24 hours rather than two.

Intranasal sumatriptan is less effective than subcutaneous injection in relieving pain in the great majority of cluster headache patients based on an open randomized study comparing the effectiveness and satisfaction of subcutaneous sumatriptan 6 mg versus intranasal sumatriptan 20 mg. Forty-nine of 52 treatments with injection resulted in complete relief of pain within 15 minutes with a mean time-to-pain relief of 9.6 minutes.[7] The remaining three attacks were reduced by a mean of 87% at 15 minutes. By comparison, only seven of 52 treatments with nasal spray in the nostril ipsilateral to the pain resulted in complete relief within 15 minutes, with a mean of 13 minutes. No pain relief was obtained in 27 attacks at 15 minutes.

These findings were confirmed by a randomized, placebo-controlled, double-blind study, which compared 20 mg intranasal sumatriptan to placebo.[8] One-hundred eighteen patients were enrolled and 154 cluster attacks were treated: 77 attacks with sumatriptan and 77 with placebo. At 30 minutes, 57% of attacks treated with sumatriptan responded and 47% were aborted completely, compared with 26% responding with placebo and 18% becoming pain free.

Sumatriptan has not been shown to be effective when taken in an attempt to prevent an oncoming attack, nor has it proven to be useful as a prophylactic agent. The overall efficacy of sumatriptan has been reported to be ~8% less in patients with chronic cluster headache than in patients with episodic cluster headache.[6] Although generally well tolerated, sumatriptan is contraindicated in patients with ischemic heart disease, variant angina, cerebrovascular and peripheral vascular disease, and uncontrolled hypertension. Consequently, particular caution must be exercised when using triptans in patients with cluster headache because the disorder most commonly affects middle-aged men, often with a history of tobacco use and other vascular risk factors.

Dihydroergotamine

Dihydroergotamine (DHE) is available in the United States in injectable and intranasal formulations. DHE-45 administered intravenously frequently provides pain relief from cluster headache within 15 minutes. The intramuscular and subcutaneous routes of administration provide slower relief because of the lower bioavailability and time to maximal concentration. Because of the rapid time to peak intensity and relatively short duration of each cluster headache attack, DHE is less practical than sumatriptan because of the necessity of needing to have an intravenous line

placed. In addition, it is not a reasonable long-term treatment plan, as the attacks are often daily and multiple during a cluster period which may last months, particularly if prophylactic therapy is not optimal or effective.

Zolmitriptan

Zolmitriptan was found to be an effective oral agent for the acute treatment of cluster headache in a double-blind controlled trial comparing the efficacy of 5 and 10 mg oral zolmitriptan to placebo.[9] With headache response defined as a 2-point reduction on a 5-point pain intensity scale, at 30 minutes, response rates following placebo, 5 and 10 mg of zolmitriptan were 29%, 40%, and 47%, respectively. The difference reached statistical significance for 10 mg zolmitriptan compared with placebo. In addition, significantly more patients reported mild or no pain 30 minutes after treatment with 5 and 10 mg zolmitriptan (57% and 60%, respectively) than following placebo (42%).

Although these efficacy rates do not approach that of oxygen or subcutaneous sumatriptan, zolmitriptan is the first orally administered triptan to demonstrate efficacy in the treatment of cluster headache and remains a therapeutic option in patients who cannot tolerate oxygen or subcutaneous sumatriptan or for those in whom an oral medication is desired.

More recently, two randomized, placebo-controlled, double-blind crossover studies looked into the efficacy of intranasal zolmitriptan at 5 and 10 mg doses. The first study involved 69 individuals with cluster headache and looked at headache response at 30 minutes.[10] In those with episodic cluster, there was a 30% response to placebo, 47% response to 5 mg, and 80% response to 10 mg; in patients with chronic cluster, the response rate at 30 minutes dropped to 14% to placebo, 28% to 5 mg, and 36% to 10 mg. The second study had 52 patients and a total of 151 treated attacks,[11] and confirmed 5 and 10 mg doses of intranasal zolmitriptan to be superior to placebo at 30 minutes, with responses being 20% to placebo, 38.5% to 5 mg, and 46.9% to 10 mg. The medication was well-tolerated in both studies.

Lidocaine

As cocainization of the sphenopalatine ganglion has been helpful in aborting cluster headache attacks, intranasal lidocaine has been utilized as an adjunctive therapy. Whether applied via a spray bottle or by dropping 4% viscous lidocaine in the nostril ipsilateral to the pain, this therapy achieves only a moderate reduction in pain in less than one-third of patients, making it useful as an adjunctive but not as "stand-alone" therapy for relief of acute cluster attacks.

PREVENTIVE PHARMACOTHERAPY

Individual cluster attacks often occur daily for several weeks to months during cluster periods, thus finding an effective preventive treatment is of paramount importance. Many patients have more than one attack per day (up to eight), and the attacks are severe, short-lived, and peak rapidly, making repeated attempts at abortive therapy an exhaustive exercise. Moreover, in a given patient, abortive therapies may be contraindicated, ineffective, not tolerated, or they may simply delay the attack. Treating frequent daily attacks can lead to overmedication or toxicity; repeated attacks of severe pain may unnecessarily prolong suffering.

The primary goals of preventive therapy are to promptly halt attacks and to sustain that remission over the anticipated duration of the cluster period. Secondary objectives are to reduce the headache frequency, as well as attack severity and duration. Bearing these primary and secondary goals in mind, preventive therapies can best be grouped into transitional and maintenance regimens.

Transitional Prophylaxis

ERGOTAMINE DERIVATIVES

Both ergotamine tartrate (2 mg) and DHE-45 (1 mg) are effective agents for achieving rapid suppression of attacks when administered daily for a short period. Patients often tolerate these medications for 2 to 3 weeks and there does not appear to be a risk of rebound in this group of patients. Ergotamine tartrate is more convenient because of its oral route of administration and may be particularly useful when given 1 to 2 hours prior to bedtime for attacks that occur predominantly or exclusively during sleep. Both agents may also be administered in divided daily doses (not to exceed 4 mg ergotamine tartrate or 3 mg DHE) when attacks are multiple or occur throughout the day. Both of these agents are contraindicated in patients with peripheral vascular disease, coronary artery disease, uncontrolled hypertension, and during pregnancy. They should not be used for the duration of the cluster period and are not intended for long-term preventive use. They also limit the abortive and long-term preventive options available because their use is contraindicated within 24 hours of using a triptan, and they are generally not administered concomitantly with methysergide because of the risk for potentiating the vasoconstrictive effects of these drugs.

CORTICOSTEROIDS

Corticosteroids (prednisone and dexamethasone) are the most rapid-acting of the prophylactic agents. They are extremely effective in rapidly suppressing attacks, while allowing time for the longer-acting maintenance drugs to take effect because the maximum benefit from other

preventive drugs may not be realized until 2 weeks after treatment is begun. Although the data are limited and uncontrolled, the largest open label study reported marked relief of cluster headache in 77% of 77 patients with episodic cluster headache and partial relief in another 12% of patients treated with prednisone.[12] With prednisone, treatment is usually initiated with 60 mg/day for 3 days followed by 10 mg decrements every 3 days over an 18-day period. A short burst of dexamethasone followed by a rapid taper could also be used.

Alternatively, greater occipital nerve blockade, using 2.5 cc 0.5% bupivacaine combined with 20 mg methylprednisolone, can be effective in up to two-thirds of cluster headache patients when performed on the side ipsilateral to the pain.[13] One randomized, double-blind, placebo-controlled study with 23 cluster headache patients found a greater suboccipital steroid injection to completely suppress attacks in more than 80% of patients, when compared with saline injection, with the majority achieving remission for at least 4 weeks.[14]

In one open label prospective study of 13 episodic cluster headache patients, all patients noted a significant decrease in headache frequency after the administration of a single dose of 30 mg/kg body weight intravenous methylprednisolone, with 23% experiencing complete remission of that cluster period.[15] Similar to what was previously known,[16–19] these findings suggest that steroids can interrupt a cluster period, but few individuals achieve complete attack remission. Steroids are mainly utilized to induce a swift remission in patients with episodic cluster headache. Although they may provide a short reprieve for those with chronic cluster headache, their continued use in these individuals is generally discouraged due to systemic side effects.

Maintenance Prophylaxis

Maintenance prophylaxis refers to the use of preventive medications throughout the anticipated duration of the cluster period. They are started at the very onset of the cluster period in conjunction with either corticosteroids or ergotamine derivatives, but are continued after these initial suppressive agents are discontinued.

VERAPAMIL

Verapamil is considered by many as the preventive therapy of choice in both episodic and chronic cluster headache, as it is effective, generally well tolerated, and can be used safely in conjunction with sumatriptan, ergotamine, corticosteroids, and other preventive agents. In a double-blind placebo-controlled trial that evaluated the efficacy of verapamil 360 mg (three divided dosages) over a 14-day period, a statistically significant reduction in headache frequency and analgesic consumption was observed versus placebo with the greatest reduction in the second week of treatment.[20]

The initial starting daily dosage is usually 80 mg three times a day (TID) or 240 mg sustained release per day. Dosages employed range from 240 to 720 mg/day in divided doses. Both the regular and extended-release preparations have been shown to be useful, and delayed release verapamil at dosages up to 720 mg may be effective in cases of refractory cluster headache. Because of this apparent dose–response relationship, a total daily dose of 480 to 720 mg is recommended before the medication is deemed a failure. Constipation is the most common side effect, but dizziness, edema, nausea, fatigue, hypotension, and bradycardia may also occur. In addition, due to the risk of heart block, it is recommended that in patients with total daily doses of 480 mg and higher, an electrocardiogram (ECG) be obtained after an 80 mg increment.

LITHIUM CARBONATE

Although the beneficial effects of lithium carbonate therapy for cluster headache prevention have been derived mainly from open clinical trials, this drug is considered to be an effective agent for cluster headache prophylaxis. Collectively, in over 28 clinical trials involving 468 patients, good to excellent results were observed in 78% of patients with chronic cluster headache.[21] The efficacy of lithium in patients with chronic cluster also appears to be durable up to 4 years after treatment. Upon interruption or cessation of therapy with lithium in this group, a transition from chronic to episodic cluster headache has been recognized.[21]

Although somewhat less robust than the response in patients with chronic cluster headache, lithium has been shown to induce a remission in 63% of 164 patients with episodic cluster.[21] A double-blind crossover study comparing verapamil (360 mg daily) and lithium (900 mg daily) in 30 patients claimed equal efficacy for the two drugs.[22] On the other hand, a separate double-blind placebo-controlled trial failed to show superiority of lithium (800 mg sustained release) over placebo. This study, however, was terminated one week after treatment began and there was an unexpectedly high placebo response rate of 31%.[23] The treatment period was therefore too short to be conclusive. The initial starting daily dosage is either 300 mg TID or 450 mg sustained release. Again, trials comparing the two formulations are not available, but a long half-life affords the option of a once daily dosage regimen, which is simpler and may enhance compliance.

Lithium is often effective at serum concentrations less than that usually required for the treatment of bipolar disorder (0.4–0.8 mEq/L), with most patients benefiting from doses of 600 to 900 mg/day. Lithium has the potential for many side effects, however, and has a narrow therapeutic window. The serum concentration should be measured 12 hours after the last dose and should not exceed more than 1.0 mEq/L. Renal and

thyroid function must be measured prior to and during treatment, and side effects such as tremor, diarrhea, and polyuria must be monitored. Caution must be exercised when lithium is coadministered with other medications, such as diuretics and nonsteroidal antiinflammatory drugs (NSAIDs).

METHYSERGIDE

Methysergide is a potent prophylactic drug for the treatment of cluster headache, but because of the potential for fibrotic complications, it is not commonly employed for long periods (>3 months) in patients with chronic cluster headache, and is no longer available in the United States. In patients with episodic cluster headache, good to excellent results have been demonstrated in 70% of patients, but the drug appears to lose its effectiveness with repeated use in up to 20% of patients.

Methysergide is a prodrug of methylergometrine, and thus should be used with caution in patients receiving other ergotamine derivatives or vasoconstrictive agents. The short-term side effects include nausea, muscle cramps, abdominal pain, and pedal edema. Long-term side effects include fibrosis of the retroperitoneum or pleural and pericardial lining. The daily dose employed is usually 2 mg in three divided doses, but up to 12 mg may be used if tolerated.

ANTIEPILEPTIC DRUGS AND CLUSTER HEADACHE PREVENTION

The pain related to cluster headache attacks has been correlated with activation of pain-producing trigeminal afferents and second-order neurons of the trigeminocervical complex, within the lower medulla and upper cervical horn.[24] Some recent studies have shown that gamma-aminobutyric acid type A ($GABA_A$) receptors may at least partly modulate the pain input to the trigeminocervical complex. For example, in a cat model, midazolam administered intravenously led to a dose-dependent inhibition of nociceptive input to the trigeminal afferents; this response was antagonized by flumazenil.[25] These findings suggest that there is a role for medications that enhance GABA in the management of cluster headache, such as valproic acid, topiramate, and gabapentin.[26] Moreover, there is evidence that neuronal transmission at trigeminal nucleus caudalis can be blocked by antagonizing glutamate activity at α-amino-3-hydroxy-5-methylisoxazole-4-proprionate (AMPA) receptors.[27,28] By their effect on voltage gated sodium and calcium channels, valproic acid, topiramate, and gabapentin may inhibit glutamate release.[29]

VALPROIC ACID

An open label study with 26 patients (21 patients with chronic cluster and five with episodic cluster) found a mean decrease of 54% of headache frequency in patients with chronic cluster and 59% in those with episodic cluster after treatment with valproic acid.[30] Average doses used were 826 mg/day in chronic cluster and 850 mg/day in episodic cluster. A retrospective review of 49 patients with cluster headache receiving valproic acid as either monotherapy or adjunctive therapy (500–1500 mg/day) found that valproic acid was efficacious in 73% of patients.[31] Another open label study in 15 patients with cluster headache demonstrated efficacy of valproic acid (600–2000 mg) with a 73% favorable response rate.[32] Nine of 15 patients had complete suppression of attacks, and the time to pain relief was brief, ranging from 1 to 4 days. Treatment was well tolerated with only nausea reported, but weight gain, hair loss, tremor, and lethargy are other commonly reported potential side effects. It has been suggested that patients whose cluster headaches are accompanied by migrainous features such as nausea, vomiting, photophobia, and phonophobia, may preferentially respond to valproic acid.

The medication is usually started in divided dosages of 250 mg twice daily (BID), and 250 mg increments per dose are recommended to find the lowest effective dose so as to minimize side effects. Pancreatitis, platelet dysfunction, thrombocytopenia, and hepatic dysfunction have been described with this medication thereby necessitating baseline and follow-up complete blood counts and liver function testing.

TOPIRAMATE

In one open label study, treatment with topiramate was associated with rapid improvement in 10 cluster headache patients.[33] Cluster period remission occurred within 1 to 3 weeks in nine patients, two of whom had chronic cluster headache. All patients responded to relatively small dosages ranging between 50 to 125 mg per day in two divided doses, which were reportedly well tolerated. Starting at low doses (25–50 mg per day), and making small increments (25–50 mg every 5–7 days) can minimize both the total daily dosage and the potential for side effects. Somnolence, dizziness, ataxia, and cognitive symptoms are the most common side effects reported by patients. Additionally, because of the weak carbonic anhydrase inhibition of this drug, renal calculi and paresthesias have also been reported. Although open-label studies with topiramate in cluster headache have not been followed up with more stringent research protocols, the drug is widely used in the management of primary headache disorders including cluster.[34] In a recent review, topiramate in dosages ranging from 50 to 200 mg was associated with reduction in cluster headache.[35]

GABAPENTIN

There is limited clinical information supporting the efficacy of gabapentin in treating cluster headache. In one open label trial, 12 patients with otherwise medically refractory cluster headache (eight with episodic cluster

and four with chronic cluster) were treated with gabapentin, starting at a dose of 100 mg/day and increased to 300 mg TID after 3 days.[36] All 12 patients were rendered pain-free within 8 days of starting gabapentin, and only mild side effects (drowsiness) were reported. A recent prospective open-label trial from Germany investigated the use of gabapentin as adjunctive therapy in eight chronic cluster patients; at doses of 800 to 3600 mg per day, 75% (six patients) had at least a 50% reduction in attacks, with the longest pain-free interval being 18 months.[37] Despite the lack of hard data, gabapentin may be a reasonable treatment option in patients who do not respond to verapamil, particularly given its potential side-effect profile compared with methysergide and lithium.

MELATONIN

Melatonin, under the regulation of the hypothalamic suprachiasmatic nucleus, is the most sensitive surrogate marker of circadian rhythm in humans. Serum melatonin levels are reduced in patients with cluster headache, particularly during a cluster period.[38] Because of these findings, the striking circadian nature of cluster headache, and the importance of the hypothalamus in the pathogenesis of this disorder, the efficacy of 10 mg oral melatonin has been evaluated in a double-blind placebo controlled trial.[39] Cluster headache remission within 3 to 5 days was achieved in five of 10 patients who received melatonin; none of the patients (10 patients) who received a placebo had remission.

INDOMETHACIN

Although chronic and episodic paroxysmal hemicrania respond dramatically to indomethacin, this medication has not been evaluated in a systematic fashion for the prophylaxis of cluster headache. Although anecdotal evidence suggests that some cluster headache patients respond to indomethacin, the response rate appears to be far less than that seen with the other TACs.

OTHERS

Capsaicin has been shown to be superior to placebo in reducing attack frequency and severity in a double-blind study when delivered at a dose of 0.025% BID via a cotton-tipped applicator in the ipsilateral nostril for 7 days. However, as there are more effective and easily administered agents available, this medication is not widely used to treat cluster headache.

Small open label studies and case reports have demonstrated efficacy of several other medications in patients with cluster headache. These include methylphenidate, antispasticity drugs (tizanidine and baclofen), clonidine, diltiazem, flunarizine, histamine, somatostatin, dopamine agonists, and pizotifen. These is a paucity of experience with these drugs and because of the lack of data, further evidence is needed before recommendations can be made to support their routine use in cluster headache. Regardless, consideration of all medical options should be given in patients with treatment-resistant cluster headache before an ablative surgical procedure is attempted.

Refractory Patients

MEDICAL THERAPY

Approximately 10% of patients develop chronic cluster headache, which does not respond to monotherapy. In addition, patients with episodic cluster headache with frequent cluster periods may develop resistance, intolerance, or contraindications to prophylactic and/or abortive medications and may require a more definitive surgical procedure for pain control.

Prior to contemplating surgery, it is worthwhile to consider adding a second or third drug, as some do better on combination therapy rather than maximal dosages of one medication alone. For many people, however, this plan is often not viable in the long-term as the toxicity of these medications may become cumulative and the side effects intolerable. In addition, ergotamine is not recommended for long-term use and the use of lithium, ergotamine, or methysergide may restrict the usage of sumatriptan as an abortive agent. Melatonin may be a useful adjunct in such a situation as there are minimal side effects, and its chronic use appears to be associated with few adverse events.

Repetitive intravenous DHE administered in an inpatient setting over 3 days may be very helpful in some patients with episodic or chronic cluster headache. In one study of 54 intractable cluster headache patients (31 of whom had chronic cluster headache), after a median hospital stay of 6 days, all patients were headache free after repetitive intravenous DHE; at 12 months follow-up, 83% and 39% of episodic and chronic cluster headache patients, respectively, remained free of headache.[40]

Histamine "desensitization" has been used to treat patients with intractable cluster headache with mixed results. Most headache medicine specialists do not use it. This therapy usually entails a prolonged hospital stay of at least one week with repetitive administration of intravenous histamine; therefore, it is not commonly used.[41]

SURGERY

For the most intractable patients who have failed outpatient and inpatient therapy, or for whom contraindications or intolerance limits the use of effective medications, surgery may be a feasible option in carefully selected patients. Following clearance from a personality and psychological profile standpoint, only patients whose headaches have been exclusively unilateral should be considered for surgery, as patients whose attacks have

alternated sides are at risk for a contralateral recurrence after surgery.

Although a wide variety of surgical procedures have been utilized, those that are directed toward the sensory trigeminal nerve have been the most successful. The ablative procedure of choice is radiofrequency thermocoagulation of the trigeminal ganglion rather than glycerol gangliorhizolysis, because the extent and precision of the lesion can be better controlled. The risk of aseptic meningitis or subarachnoid hemorrhage is also higher with glycerol gangliorhizolysis.

The overall response to radiofrequency rhizotomy is encouraging with ~75% of patients reporting good to excellent results. The durability of the procedure is also quite favorable with only a 20% long-term recurrence rate; some patients remain pain free even after 20 years.[42] The best results may require complete analgesia or dense hypalgesia. If the pain is primarily orbital in location, V1 and V2 lesions appear to be adequate, but if the pain also involves the temporal or auricular region, a V3 lesion may also be necessary for optimal results. Indeed, in those patients whose pain is primarily located around the ear, temple, or cheek, an ablative trigeminal procedure may not be curative or as successful. Transient complications may include diplopia, hyperacusis, ice-pick pain, and jaw deviation. Long-term complications include corneal anesthesia and in less than 4% of cases, anesthesia dolorosa. Aggressive long-term ophthalmic follow-up and eye care is critically important.

Effective relief of medically refractory cluster headache with gamma knife radiosurgery was reported in six patients.[43] The time to effective relief was either immediate or within one week. Four patients were pain free at more than 8 months follow-up. However, these results have not yet been borne out by subsequent studies, which found that patients with intractable cluster headache can have adequate pain relief in the short-term, but these benefits were not long-lasting.[44,45] Consequently, the overall efficacy, safety, and durability of this procedure remain unclear.

Several authors have reported satisfactory results in patients with refractory chronic cluster headache after section of the sensory trigeminal nerve at the root exit zone.[46,47] Trigeminal sensory rhizotomy via a posterior fossa approach was employed by Onofrio and Campbell in 10 patients with relief of pain in six and no improvement in four patients. In the largest series, Kirkpatrick and colleagues reported complete or near complete relief of pain in 12 of 14 patients who underwent a sensory trigeminal rhizotomy using a similar approach. The mean duration of follow-up was 5.6 years. Only one patient developed a contralateral recurrence of attacks. Seven patients who had a partial nerve root section required a second procedure for complete resection. They concluded that a complete section was more likely to provide relief than a partial section, but agreed with the findings of others that total loss of sensation of all three divisions of the trigeminal nerve did not guarantee relief from the attacks.

OCCIPITAL NERVE STIMULATION

In 1999, occipital nerve stimulation (ONS) was introduced as a potential treatment for intractable primary headache disorders.[48] Since that time, numerous other studies have shown ONS to be effective in the management of intractable cluster headache.[49–53] In one recent study from the National Hospital in London, United Kingdom, eight patients with medically intractable chronic cluster headache were offered occipital nerve stimulation and followed for an average of 20 months.[51] Six of the patients (75%) found the ONS to be helpful in reducing the frequency and severity of their attacks with two reporting substantial improvement (90–95%), three reporting moderate improvement (40%, 60%, and 20–80%), and one noting mild (25%) improvement. In a second study published earlier this year, 14 patients with medically intractable chronic cluster headache were treated with ONS[52]; at median follow up of 17.5 months, 10 individuals (71%) reported improvement, with three patients perceiving marked improvement, three patients moderate improvement, and four patients mild improvement in their attacks. Researchers from Belgium demonstrated the efficacy of ONS in another prospective pilot study, where eight medically refractory cluster headache patients had an occipital nerve stimulator implanted on the side of the headache.[54] All but one patient was able to significantly reduce their prophylactic medication regimen, due to significant benefit from the ONS. At follow-up of 16 and 22 months, two patients were pain free, three had 90% cluster attack reduction, and two had 40% improvement. In all studies, patients documented clinical deterioration when the ONS malfunctioned or the battery was depleted. Side effects were minimal and consisted of lead migration or battery depletion, suggesting ONS implantation could be a less invasive and safer alternative to hypothalamic deep brain stimulation. The majority of the individuals who found headache relief with ONS stated they would recommend the procedure to others.

The mechanism by which ONS affords headache relief is not clear, but several theories have been proposed. Functional imaging studies have demonstrated effects on central pain-modulating centers.[55] Furthermore, ONS may directly impact nociceptive neuronal activity within the trigeminal nucleus caudalis.[56]

DEEP BRAIN STIMULATION

Hypothalamic dysfunction has been implicated as the central generator of cluster headache, with the pain and autonomic features developing as cranial parasympathetic efferent and first division nociceptive neurons are activated.[57] A recent study found hypothalamic

deep brain stimulation (DBS) to be effective in nearly 60% of medically refractory chronic cluster headache sufferers, suggesting this may be a promising option for those who have failed all other treatments.[58] However, a recently published randomized placebo-controlled doubled-blind study from France demonstrated DBS not to be effective.[59] In this trial, 11 patients with medically intractable cluster headache underwent DBS electrode implantation into the posterolateral hypothalamus, and the patients were randomly assigned to either have the stimulator turned on for a month then off (five patients) or vice versa (six patients). The investigators found no difference in weekly cluster attack frequency between the "stimulator on" and the "stimulator off" periods. All patients then underwent a 12-month unblinded period, with the stimulators turned on and able to be adjusted. At the 1-year mark, three patients were nearly attack free, four had >50% improvement in attack frequency, and the remaining four patients did not experience significant benefit. Although the open phase of this study maintained the idea that DBS may be effective for cluster headache with 60% of their subjects having a positive response during that time, the randomized phase did not support this.

REFERENCES

1. Irimia P, Cittadini E, Paemeleire K, Cohen AS, Goadsby PJ. Unilateral photophobia or phonophobia in migraine compared with trigeminal autonomic cephalalgias. Cephalalgia 2008; 28(6):626–630
2. Wilbrink LA, Ferrari MD, Kruit MC, Haan J. Neuroimaging in trigeminal autonomic cephalgias: when, how, and of what? Curr Opin Neurol 2009;22(3):247–253
3. Akerman S, Holland PR, Lasalandra MP, Goadsby PJ. Oxygen inhibits neuronal activation in the trigeminocervical complex after stimulation of trigeminal autonomic reflex, but not during direct dural activation of trigeminal afferents. Headache 2009;49(8):1131–1143
4. Ekbom K; The Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. N Engl J Med 1991;325(5):322–326
5. Ekbom K, Krabbe A, Micieli G, et al. Cluster headache attacks treated for up to three months with subcutaneous sumatriptan (6 mg). Cephalalgia 1995;15:230–236
6. Göbel H, Lindner V, Heinze A, Ribbat M, Deuschl G. Acute therapy for cluster headache with sumatriptan: findings of a one-year long-term study. Neurology 1998; 51(3):908–911
7. Hardebo JE, Dahlöf C. Sumatriptan nasal spray (20 mg/dose) in the acute treatment of cluster headache. Cephalalgia 1998;18(7):487–489
8. van Vliet JA, Bahra A, Martin V, et al. Intranasal sumatriptan in cluster headache: randomized placebo-controlled double-blind study. Neurology 2003;60(4):630–633
9. Bahra A, Gawel MJ, Hardebo JE, et al. Oral zolmitriptan is effective in the acute treatment of cluster headache. Neurology 2000;54(9):1832–1839
10. Cittadini E, May A, Straube A, Evers S, Bussone G, Goadsby PJ. Effectiveness of intranasal zolmitriptan in acute cluster headache: a randomized, placebo-controlled, double-blind crossover study. Arch Neurol 2006;63(11):1537–1542
11. Rapoport AM, Mathew NT, Silberstein SD, et al. Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study. Neurology 2007;69(9):821–826
12. Kudrow L. Cluster Headache: Mechanisms and Management. Oxford/New York: Oxford University Press; 1980
13. May A, Leone M, Afra J, et al; EFNS Task Force. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. Eur J Neurol 2006;13(10): 1066–1077
14. Ambrosini A, Vandenheede M, Rossi P, et al. Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. Pain 2005;118(1-2):92–96
15. Antonaci F, Costa A, Candeloro E, Sjaastad O, Nappi G. Single high-dose steroid treatment in episodic cluster headache. Cephalalgia 2005;25(4):290–295
16. Cianchetti C, Zuddas A, Marchei F. High dose intravenous methylprednisolone in cluster headache. J Neurol Neurosurg Psychiatry 1998;64(3):418
17. Prusinski A, Kozubski W, Szulc-Kuberska J. Steroid treatment in the interruption of clusters in cluster headache. Cephalalgia 1987;6:332–333
18. Couch JR Jr, Ziegler DK. Prednisone therapy for cluster headache. Headache 1978;18(4):219–221
19. Jammes JL. The treatment of cluster headaches with prednisone. Dis Nerv Syst 1975;36(7):375–376
20. Leone M, D'Amico D, Attanasio A, et al. Verapamil is an effective prophylactic for cluster headache: results of a double-blind multicenter study versus placebo. In: Olesen J, Goadsby PJ, eds. Cluster Headache & Related Conditions. Oxford/New York: Oxford University Press; 1999:296–299
21. Ekbom K. Lithium for cluster headache: review of the literature and preliminary results of long-term treatment. Headache 1981;21(4):132–139
22. Bussone G, Leone M, Peccarisi C, et al. Double blind comparison of lithium and verapamil in cluster headache prophylaxis. Headache 1990;30(7):411–417
23. Steiner TJ, Hering R, Couturier EGM, Davies PT, Whitmarsh TE. Double-blind placebo-controlled trial of lithium in episodic cluster headache. Cephalalgia 1997;17(6): 673–675
24. Dodick DW, Rozen TD, Goadsby PJ, Silberstein SD. Cluster headache. Cephalalgia 2000;20(9):787–803
25. Storer RJ, Akerman S, Shields KG, Goadsby PJ. GABAA receptor modulation of trigeminovascular nociceptive neurotransmission by midazolam is antagonized by flumazenil. Brain Res 2004;1013(2):188–193
26. Pascual J, Láinez MJA, Dodick DW, Hering-Hanit R. Antiepileptic drugs for the treatment of chronic and episodic cluster headache: a review. Headache 2007;47(1):81–89
27. Storer RJ, Goadsby PJ. Trigeminovascular nociceptive transmission involves N-methyl-D-aspartate and non-N-methyl-D-aspartate glutamate receptors. Neuroscience 1999;90(4): 1371–1376
28. Mitsikostas DD, Sanchez del Rio M, Waeber C, Huang Z, Cutrer FM, Moskowitz MA. Non-NMDA glutamate receptors modulate capsaicin induced c-fos expression within trigeminal nucleus caudalis. Br J Pharmacol 1999;127(3): 623–630

29. Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. Nat Med 2004;10(7):685–692
30. Freitag FG, Diamond S, Diamond ML, Urban G, Peepr B. Divalproex sodium in the preventive treatment of cluster headache. Headache 2000;40:408–411
31. Gallagher RM, Mueller LL, Freitag FG. Divalproex sodium in the treatment of migraine and cluster headaches. J Am Osteopath Assoc 2002;202:92–94
32. Hering R, Kuritzky A. Sodium valproate in the treatment of cluster headache: an open clinical trial. Cephalalgia 1989; 9(3):195–198
33. Wheeler SD, Carrazana EJ. Topiramate-treated cluster headache. Neurology 1999;53(1):234–236
34. Cohen AS, Matharu MS, Goadsby PJ. Trigeminal autonomic cephalalgias: current and future treatments. Headache 2007;47(6):969–980
35. Pascual J, Láinez MJ, Dodick D, Hering-Hanit R. Antiepileptic drugs for the treatment of chronic and episodic cluster headache: a review. Headache 2007;47(1):81–89
36. Leandri M, Luzzani M, Cruccu G, Gottlieb A. Drug-resistant cluster headache responding to gabapentin: a pilot study. Cephalalgia 2001;21(7):744–746
37. Schuh-Hofer S, Israel H, Neeb L, Reuter U, Arnold G. The use of gabapentin in chronic cluster headache patients refractory to first-line therapy. Eur J Neurol 2007;14(6): 694–696
38. Leone M, Lucini V, D'Amico D, et al. Twenty-four-hour melatonin and cortisol plasma levels in relation to timing of cluster headache. Cephalalgia 1995;15(3):224–229
39. Leone M, D'Amico D, Moschiano F, Fraschini F, Bussone G. Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. Cephalalgia 1996;16(7):494–496
40. Mather PJ, Silberstein SD, Schulman EA, Hopkins MM. The treatment of cluster headache with repetitive intravenous dihydroergotamine. Headache 1991;31(8):525–532
41. Diamond S, Freitag FG, Prager J, Gandhi S. Treatment of intractable cluster. Headache 1986;26(1):42–46
42. Taha JM, Tew JM Jr. Long-term results of radiofrequency rhizotomy in the treatment of cluster headache. Headache 1995;35(4):193–196
43. Ford RG, Ford KT, Swaid S, Young P, Jennelle R. Gamma knife treatment of refractory cluster headache. Headache 1998;38:3–9
44. McClelland SIII, Tendulkar RD, Barnett GH, Neyman G, Suh JH. Long-term results of radiosurgery for refractory cluster headache. Neurosurgery 2006;59(6):1258–1262, discussion 1262–1263
45. McClelland SIII, Barnett GH, Neyman G, Suh JH. Repeat trigeminal nerve radiosurgery for refractory cluster headache fails to provide long-term pain relief. Headache 2007;47(2): 298–300
46. Onofrio BM, Campbell JK. Surgical treatment of chronic cluster headache. Mayo Clin Proc 1986;61(7):537–544
47. Kirkpatrick PJ, O'Brien MD, MacCabe JJ. Trigeminal nerve section for chronic migrainous neuralgia. Br J Neurosurg 1993;7(5):483–490
48. Weiner RL, Reed KL. Peripheral neurostimulation for control of intractable occipital neuralgia. Neuromodulation 1999;2:217–221
49. Schwedt TJ, Dodick DW, Trentman TL, Zimmerman RS. Occipital nerve stimulation for chronic cluster headache and hemicrania continua: pain relief and persistence of autonomic features. Cephalalgia 2006;26(8):1025–1027
50. Schwedt TJ, Dodick DW, Hentz J, Trentman TL, Zimmerman RS. Occipital nerve stimulation for chronic headache—long-term safety and efficacy. Cephalalgia 2007;27(2):153–157
51. Burns B, Watkins L, Goadsby PJ. Treatment of medically intractable cluster headache by occipital nerve stimulation: long-term follow-up of eight patients. Lancet 2007;369(9567): 1099–1106
52. Burns B, Watkins L, Goadsby PJ. Treatment of intractable chronic cluster headache by occipital nerve stimulation in 14 patients. Neurology 2009;72(4):341–345
53. Bartsch T, Paemeleire K, Goadsby PJ. Neurostimulation approaches to primary headache disorders. Curr Opin Neurol 2009;22(3):262–268
54. Magis D, Allena M, Bolla M, De Pasqua V, Remacle JM, Schoenen J. Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study. Lancet Neurol 2007;6(4):314–321
55. Matharu MS, Bartsch T, Ward N, Frackowiak RS, Weiner R, Goadsby PJ. Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. Brain 2004;127(Pt 1):220–230
56. Goadsby PJ, Bartsch T, Dodick DW. Occipital nerve stimulation for headache: mechanisms and efficacy. Headache 2008;48(2):313–318
57. May A. Hypothalamic deep-brain stimulation: target and potential mechanism for the treatment of cluster headache. Cephalalgia 2008;28(7):799–803
58. Leone M. Deep brain stimulation in headache. Lancet Neurol 2006;5(10):873–877
59. Lanteri-Minet M, Fontaine D, Fabre N, et al. Refractory chronic cluster headache treated by deep brain stimulation: a French multicentric randomized placebo-controlled double-blind trial. Neurology 2009;72(11, Suppl 3):A252