Management of Cluster Headache

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Cluster headache, an excruciating, unilateral headache usually accompanied by conjunctival injection and lacrimation, can occur episodically or chronically, and can be difficult to treat. Existing effective treatments may be underused because of underdiagnosis of the syndrome. Oxygen and sumatriptan have been demonstrated to be effective in the acute treatment of cluster headaches. Verapamil has been shown to be effective for prophylaxis. For cluster headache completely refractory to all treatments, surgical modalities and newer interventions such as the implantation of stereotactic electrodes may be useful. Patients should be encouraged to avoid possible triggers such as smoking or alcohol consumption, especially during the cluster period. The intensity of cluster headache pain leads to ethical concerns among researchers over the use of placebo, making randomized controlled trials difficult. As new technology and genetic studies clarify the etiology of cluster headache, it is possible that more specific therapies will emerge. (Am Fam Physician 2005;71:717-24,728. Copyright© 2005 American Academy of Family Physicians.)

▶ **Patient information:** A handout on cluster headaches, written by the authors of this article, is provided on page 728.

See page 639 for strength-of-recommendation labels.

The diagnosis and optimal management of cluster headache remain challenging. This most painful of primary headaches affects 0.1 percent of adults.[1] The male-to-female ratio has diminished from 6.2 to 1 in the 1960s to 2.1 to 1 in the 1990s.[2] Men may first experience cluster headache in their early 20s, with peak onset in their 40s. In one study,[3] the most frequent age at onset for women was in their 60s. Cluster headache may be underdiagnosed in black women,[4] but ethnic differences in prevalence have not been studied. Having a family history of headaches, smoking, head injury, or shift work has been associated with cluster headache.

Clinical Features and Classification

In 2004, the International Headache Society published new criteria for diagnosing cluster headache. To fulfill criteria for diagnosis, patients must have had at least five attacks occurring from one every other day to eight per day; and attributable to no other disorder.[5] In addition, headaches must cause severe or very severe unilateral orbital, supraorbital, or temporal pain lasting 15 to 180 minutes if untreated, and be accompanied by one or more of the following: ipsilateral conjunctival injection or lacrimation, ipsilateral nasal congestion or rhinorrhea, ipsilateral eyelid edema, ipsilateral forehead and facial sweating, ipsilateral miosis or ptosis, or a sense of restlessness or agitation.[5] Episodic cluster headache is defined as at least two cluster periods lasting seven to 365 days and separated by pain-free remission periods of one month or longer. Chronic attacks recur over more than one year without remission or with remission lasting less than one month.[5]

Restlessness and agitated behavior are reported symptoms in 93 percent of cluster headache patients.

Called "suicide headache" because of its severity and "alarm clock" headache because of its periodicity, cluster headache is characterized by unilateral excruciating pain (a hot-poker or stabbing sensation) in the ocular, frontal, or temporal areas. Pain often radiates to the upper teeth, jaw, and neck. Associated signs include ptosis, ipsilateral lacrimation, conjunctival injection, and rhinorrhea. The pain usually is unilateral, with 60 percent of patients reporting headaches on the right side, but 14 percent of patients report a side shift during an attack, and 18 percent report involvement of different sides in subsequent attacks.[6]

Other symptoms include facial flushing or pallor, tenderness on palpation of the ipsilateral carotid artery, bradycardia, and abnormal feeling of scalp hairs. The absence of aura, nausea, or vomiting has helped distinguish cluster from migraine headaches, but recent studies indicate that 14 percent

Strength of Recommendations

Key clinical recommendation	*Label*	*References*
The first-line treatments for acute cluster headache are oxygen or sumatriptan, or a combination of the two.	A	15-18
Less well studied alternatives for acute treatment include intranasal dihydroergotamine, intranasal lidocaine, and intranasal capsaicin.	B	19-21
Verapamil, in a dosage of 360 to 480 mg daily, can effectively reduce the number of attacks during a cluster headache period.	A	24, 26
Less well studied alternatives for prophylaxis include prednisone and antiepileptic drugs; they should only be considered if verapamil is not tolerated or not effective.	B	26, 32, 28

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, opinion, or case series. See page 639 for more information.

of patients with cluster headache experience aura, 51 percent have a personal or family history of migraine, 56 percent report photophobia, 43 percent report phonophobia, and 23 percent report osmophobia.[7] Thus, the presence of aura, nausea, vomiting, or photophobia should not rule out a diagnosis of cluster headache.[8] A characteristic feature of cluster headache, noted by 93 percent of patients in one study,[7] is restlessness, with behaviors such as pacing and rocking the head and trunk with head in hands.[9] Most of these headaches last 15 minutes to three hours and recur at the same time of day, often at night. Many attacks begin during the first rapid-eye-movement sleep phase. Patients may report a seasonal pattern, with spring and autumn peaks.

Cluster headache is diagnosed by history, and the key feature is a pattern of recurrent bouts of near-daily attacks lasting for days, weeks, or months. Patients fearing an attack may be afraid to go to sleep. Precipitants of cluster headache include hypoxia, which may occur with sleep apnea. Vasodilators such as nitroglycerin, alcohol, and carbon dioxide may trigger a headache during a cluster period.[10]

Although similar to cluster headache, paroxysmal hemicrania headaches are briefer and are treated effectively with indomethacin.[5] Orbital myositis may mimic cluster headache, but the headache has a longer duration.

Etiology

Positron emission tomographic (PET) scanning and functional magnetic resonance imaging are helping to clarify the poorly understood etiology of cluster headache. The basic pathophysiology is in the hypothalamic gray matter.[11] In some families, an autosomal dominant gene may be involved, but calcium channel activity or nitric oxide sensitivity alleles have not been identified.[12] Carotid and ophthalmic artery vasodilation and an increased sensitivity to vasodilator stimuli during an attack may be triggered by trigeminal parasympathetic reflexes. Abnormal heart rate variability and increased nocturnal lipolysis during attacks and in remission reinforce the theory of an autonomic function abnormality with increased parasympathetic drive and decreased sympathetic function. Attacks often begin during sleep, implicating a disorder of circadian rhythm.[13] An increased incidence of sleep apnea in patients with cluster headache suggests that periods of reduced oxygenation of key tissues may trigger an attack.[14]

Treatment

Cluster headache treatment requires a dual strategy. Acutely, the attack must be aborted or subdued. Concurrently, prophylaxis is initiated to suppress the recurrent headaches expected throughout the remaining clus-

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TABLE 1
Treatment of Acute Cluster Headache

Drug	*Dosage and route*	*Reported adverse effects*	*Efficacy*	*Comments*
Oxygen	7 L per minute for 15 minutes via face mask	None	In a double-blind crossover study[15] of 19 patients, 56 percent reported complete or substantial relief compared with 7 percent in the placebo group.	Treatment of choice
Sumatriptan	6 mg subcutaneously; may repeat in 24 hours	Local skin reactions, fatigue, nausea, vomiting, dizziness, chest symptoms, throat symptoms, burning sensations, paresthesias	In a double-blind RCT[16] of 49 patients, 46 percent were free of pain within 15 minutes compared with 10 percent in the placebo group. In an open study[17] of 138 patients, 96 percent of attacks were relieved at 15 minutes.	Contraindicated in patients with coronary artery disease, uncontrolled hypertension, or angina
	20-mg nasal spray	None	In a double-blind RCT[18] of 118 patients, there was a 57 percent response compared with a response of 26 percent with placebo. Pain-free rates at 30 minutes were 47 percent compared with 18 percent with placebo.	—
Intranasal dihydroergotamine	0.5-mg nasal spray bilaterally	None	In a double-blind trial[19] of 25 patients, the severity of attacks was reduced. There was no effect on frequency or duration of attacks.	Intravenous and intramuscular routes have been used, but their efficacy has not been substantiated in controlled clinical trials.
Intranasal lidocaine	1 mL of 10 percent lidocaine placed with a cotton swab bilaterally for 5 minutes	Unpleasant taste	In a double-blind, placebo-controlled trial[20] of 15 patients, there was a decrease in pain after 5 minutes, and nine of nine treated patients were free of pain at 35 minutes.	Place as close to sphenopalatine fossa as possible.
Intranasal capsaicin	Place via cotton swab in ipsilateral nostril twice a day for seven days	Burning sensation (decreases after five applications)	In a double-blind, placebo-controlled trial[21] of 15 patients, there was a reduction of headache severity in the treatment group at eight to 15 days.	There were more patients with episodic cluster headache in the treatment group and more patients with chronic headache in the control group.

RCT = randomized controlled trial.

Information from references 15 through 21.

ter period; prophylaxis is continued for the expected duration of the cluster period and then tapered off. Patients with chronic cluster headache require long-term prophylaxis. In patients with intractable headaches, more aggressive intervention, including surgery, may be required.

ACUTE OR ABORTIVE

The treatments of choice for acute cluster headache are oxygen (7 L per minute for 15 minutes), sumatriptan, or a combination of the two *(Table 1)*.[15-21] Both therapies appear to be underprescribed. Sumatriptan is available as a subcutaneous injection or as a nasal spray.[16-18] It is contraindicated in patients with ischemic heart disease, uncontrolled hypertension, or peripheral vascular disease, and it should not be combined with ergotamine. Tachyphylaxis does not occur when the drug is used for long periods. Higher sumatriptan doses (12 mg subcutaneously) were not found to be more effective and had more side effects than 6-mg doses.[18]

The treatments of choice for acute cluster headache attacks are oxygen, sumatriptan, or a combination of these treatments.

Intranasal dihydroergotamine can reduce attack severity, but it does not reduce attack frequency or duration. This nasal spray has fewer adverse reactions and better bioavailability than oral ergotamine.[19] Intranasal lidocaine has been shown to decrease pain after five minutes, with nine of nine treated patients free of pain after 35 minutes.[20] Intranasal capsaicin, which is hypothesized to deplete substance P from sensory nerve terminals, is used in treatment of other pain states, including herpes zoster. In a study of patients with cluster headache, it reduced the severity of headaches after seven days of treatment.[21]

The effectiveness of melatonin is unclear because of conflicting studies.[22] Its role, if any, will be in the initial prevention of attacks, theoretically by resetting the circadian rhythm.

PROPHYLACTIC

Oral sumatriptan has not been shown to be effective prophylactically.[23] Verapamil in dosages of 360 to 480 mg daily is one of the few treatments for episodic cluster headache tested in a randomized controlled trial (RCT) and found effective in reducing attack frequency *(Table 2)*.[13,24-31] This treatment also is underused, with only 4 percent of patients with cluster headache reporting prophylactic verapamil use.

Prednisone often is used in prophylaxis, starting at a dosage of 50 to 80 mg daily and tapered over 10 to 12 days. A 1975 study that used a double-blind control methodology led to improvement in 17 of 19 patients compared with placebo, but the study quality was limited.[26] A recent nonrandomized study of cluster headache prophylaxis that used three days of 250 mg of intravenous methylprednisolone followed by a prednisone taper indicated fewer headaches in the active phase than with previous treatments in a group of 14 men.[32] In small studies, the antiepileptic drugs divalproex and topiramate were found to be useful.[28] Gabapentin and baclofen have been tried with some success in case reports and nonrandomized trials.[28] However, no RCTs have been conducted to determine conclusively the effectiveness of antiepileptic drugs.

Verapamil has demonstrated efficacy in the prophylaxis of episodic cluster headache.

Historically, ergotamine in a dosage of 2 to 4 mg per day has been a common agent for episodic prophylaxis, but no RCT of oral ergotamine has been reported. Ergotamine and sumatriptan should not be taken concur-

TABLE 2
Prophylaxis of Episodic Cluster Headaches

Drug	*Dosage and route*
Verapamil	120 to 160 mg orally three times daily
Prednisone	50 to 80 mg orally daily tapered over 10 to 12 days
Divalproex	600 to 2,000 mg daily
Topiramate	25 mg orally daily for seven days, then increase dose by 25 mg daily every week to a maximum dosage of 200 mg daily
Ergotamine	2 to 4 mg daily in divided doses
Methylergonovine maleate	0.2 mg orally three or four times daily
Melatonin	10 mg orally at bedtime

RCT = randomized controlled trial.

**—Review article; original studies not referenced.*

Information from references 13, and 24 through 31.

Adverse effects	*Efficacy*	*Comments*
Hypotension, bradycardia, atrioventricular block, dizziness, fatigue, nausea, constipation	In a double-blind RCT[24] of 30 patients, 12 of 15 patients had a reduction in frequency of attacks within two weeks. In a double-blind study[25] of 30 patients who received verapamil versus lithium, 50 percent of patients improved during first week of treatment.	—
Increased appetite, insomnia, nervousness, hyperglycemia, dizziness, headache	In a double-blind study,[26] 17 of 19 patients experienced improvement in pain, and the treatment group had a lower frequency of headaches. In a retrospective study,[27] 14 of 19 patients had more than 50 percent headache relief.	In trial,[26] improvement occurred within two days. Recurrences often occurred toward the end of the taper.[27] Should take concurrently with another prophylactic medication.
Nausea, somnolence, dizziness, insomnia, anorexia, weakness, thrombocytopenia, alopecia, weight gain	In an open-label study,[28] nine of 15 patients experienced complete disappearance of pain, and two others markedly improved. In another open-label study[28] of 26 patients, headache frequency decreased by 54 to 59 percent.* No RCTs.	Use caution in patients with renal or hepatic insufficiency.
Paresthesias, cognitive effects, drowsiness, dizziness	In a retrospective chart review[29] of patients with migraine and cluster headache, nine of 12 patients with cluster headaches exhibited moderate to substantial improvement. No RCTs.	—
Vertigo, pruritus, nausea, paresthesias, weakness, cardiac valvular fibrosis, retroperitoneal or pleuropulmonary fibrosis, angina, myocardial infarction; may cause withdrawal symptoms if suddenly discontinued	No RCTs. Anecdotal evidence by experienced neurologist suggests effectiveness.[13]	Best for nocturnal attacks; contraindicated in peripheral vascular disease, hypertension, and cardiac disease; caution with renal or hepatic insufficiency; should not take concurrently with sumatriptan
Hypertension, nausea, vomiting, diarrhea, leg cramps, dyspnea, dizziness, tinnitus, nasal congestion, diaphoresis, palpitations, thrombophlebitis, hematuria, water intoxication, abdominal cramping, weight gain, paresthesias, amenorrhea; hallucinations in high doses	In a retrospective cross-sectional study,[30] 19 of 20 patients reported a decrease of more than 50 percent in headache frequency; 15 of 20 patients reported a reduction in headache intensity.	Caution in patients with peripheral vascular disease, cardiac disease, or renal or hepatic insufficiency; only for use in refractory cases; should never be used continually for longer than six months; contraindicated in pregnant and hypertensive patients; possibility of retroperitoneal, cardiac, and pleuropulmonary fibrosis
None reported	In a double-blind, placebo-controlled study[31] of 20 patients, headache frequency was reduced in five of 10 patients in the treatment group. A more recent pilot study[19] of nine patients did not show any difference in response between the treatment and placebo groups.	—

rently. In addition, patients with peripheral vascular disease should not take ergotamine. A recent review summarizes management guidelines for patients who continue to use ergotamine or who cannot tolerate verapamil or other prophylactic medications. Patients who experience attacks at night may be given 1- or 2-mg tablets orally or by suppository before bedtime.[13] When headaches start consistently at the same time each day, patients may be advised to take ergotamine 30 to 60 minutes before the time of their usual attack. A combination of verapamil and ergotamine may be considered.[13]

TABLE 3
Treatment of Chronic Cluster Headaches

Drug	*Dosage and route*	*Adverse effects or complications*	*Efficacy*	*Generic cost**	*Comments*
Verapamil	120 mg orally three times daily	Hypotension, bradycardia, atrioventricular block, dizziness, fatigue, nausea, constipation	In an RCT of 30 patients, 12 of 15 patients had a reduction in frequency of attacks within two weeks.[25]	$20 to 46 per month	—
Lithium	Start at 300 mg orally three times daily; use blood levels to achieve therapeutic dose.	Confusion, dizziness, blurry vision, diabetes insipidus, headache, nausea, polyuria	In a double-blind crossover study[33] of 30 patients, 50 percent of patients responded in two weeks. In a more recent RCT,[34] using 800-mg extended-release tablets daily showed no benefit over placebo.	$11 to 16 per month	Need close monitoring of lithium levels; test 12 hours after last dose; side effects include tremor and dysuria; check thyroid and renal function before and during treatment.
Microvascular decompression	NA	Infection, cerebrospinal fluid leak, postoperative headache requiring lumbar puncture	In a trial[35] of 28 patients, 46 percent had success at long-term follow-up.	NA	Only used for intractable cases

NA = not applicable; RCT = randomized controlled trial.

**—Estimated cost to the pharmacist based on average wholesale prices in Red book. Montvale, N.J.: Medical Economics Data, 2004. Cost to the patient will be higher, depending on prescription filling fee.*

Information from references 25, and 33 through 35.

Methysergide previously was used for cluster headache prophylaxis, but its use has been discontinued in the United States because it can cause retroperitoneal, cardiac, and pleuropulmonary fibrosis. Methylergonovine maleate should be restricted to use in refractory cases and should never be used for more than six months continuously. Methylergonovine, probably the active metabolite of methysergide, decreased cluster headache frequency by more than 50 percent in 19 of 20 patients in a pilot study.[32] Contraindications include hypertension and pregnancy. Methylergonovine should be used with caution, if at all, in patients with cardiac or peripheral vascular disease, or hepatic or renal insufficiency. Hallucinations can occur because it is a lysergic acid derivative.[30]

CHRONIC CLUSTER HEADACHE

Verapamil is used in the treatment of chronic cluster hadache.[24] Lithium has been used as long-term prophylaxis for years on the basis of case series demonstrating effectiveness *(Table 3)*.[25,33-35] In an RCT of lithium in episodic cluster headache, substantial improvement occurred in both groups: six (43 percent) of 14 patients in the placebo group and eight (62 percent) of 13 in the lithium group. The study, which was stopped because superiority over placebo could not be demonstrated, challenges physicians to look at the positive treatment effect of placebo.[34]

SURGICAL OPTIONS FOR INTRACTABLE HEADACHE

Microvascular decompression of the fifth cranial nerve with or without section of the nervus intermedius was performed in 30 patients.[35] Initially, 77.3 percent of patients experienced relief, but after five years, only 46.6 percent reported continued excellent or good outcome. Repeat surgeries did not add benefit. It is important to choose a surgical

intervention that maintains nerve supply so that facial numbness and corneal anesthesia are less likely to occur.

NEW DIRECTIONS

Patients with severe snoring and cluster headache should be evaluated for sleep apnea. In some patients diagnosed with sleep apnea, treatment for apnea also proved to be effective for the headaches.[14]

Botulinum toxins A and B are being studied as treatments for various headaches, with evidence of some efficacy and mixed reports as to side effects. An ongoing study is addressing their role in chronic cluster headache.

A recent report[35] described a patient with intractable cluster headache; PET scanning revealed activation of the posterior inferior hypothalamic gray matter during attacks. A stereotactic electrode was implanted in this area, with a permanent generator placed in a subclavicular pocket. When stimulation was provided at a frequency of 180 Hz, the attacks disappeared after 48 hours. Twice, the stimulator was turned off without the patient's knowledge, and attacks returned within 48 hours. The latter attacks disappeared 48 hours after the generator was restarted. Thirteen months later, the pain had not recurred.

Behavior and Lifestyle Interventions

Although little research has assessed the effectiveness of psychologic and behavior strategies on cluster headache, these approaches have been supported in the management of migraine and other chronic headaches. Strategies that have proved effective for other headaches target pain intensity and resultant disability, analgesic overuse, adherence to prescribed regimens, and psychiatric comorbidity. The difference between a functional life with pain and a life of significant disability often is related to the patient's ability to pace activities and regulate emotions (thereby decreasing the fear of pain and subsequent autonomic arousal), engage in healthy behaviors, and function despite the presence of pain.

To maximize the quality of life in patients with cluster headache, strategies including relaxation, biofeedback, smoking cessation, and alcohol intake reduction should be considered. The prevalence of cigarette smoking is higher in patients with cluster headache than in control patients. In one retrospective study,[7] however, patients with cluster headache who had stopped smoking did not notice any change in their symptom pattern. Heavy alcohol use is more common in patients who progress to chronic cluster headache compared with those who have episodic headache, although it is unknown whether alcohol is a cause or result of living with chronic pain.

Relaxation training paired with thermal biofeedback is effective in tension and migraine headache treatment. Biofeedback may be effective in patients with post-traumatic headache.[36] For patients with cluster headache and a history of head trauma or migraine, these options may be considered. If cluster headache is an autonomic disorder, biofeedback may be valuable. Cognitive behavior interventions with proven value in migraine treatment[38] that may be considered in patients with cluster headache include discussing reasonable expectations, keeping simple behavior diaries, and emphasizing personal responsibility. Patients are taught self-assessment and self-regulation skills that help them challenge irrational beliefs such as all-or-nothing thinking, catastrophizing outcomes, or attributional styles that lead them toward ineffective strategies (e.g., "I have no control over the pain"). Providing patients with ongoing compassion, knowledge about cluster headache, coping skills, and a long-term trust relationship is crucial in helping them cope with this difficult and painful condition.

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