

Cluster Headache: Rapid Evidence Review

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Cluster headache, the most common form of trigeminal autonomic cephalgia, is a rare primary headache disorder that affects less than 1% of the population. The mean age of onset is 30 years, and it is two to three times more common in males. Cluster headache consists of attacks of severe unilateral pain located in the orbital, supraorbital, and/or temporal region that occur from every other day up to eight times per day and last from 15 to 180 minutes. The pain is associated with ipsilateral autonomic symptoms (most commonly lacrimation, conjunctival injection, nasal congestion or rhinorrhea, ptosis, edema of the eyelid, sweating of the forehead or face, and miosis) and a sense of agitation or restlessness. Attacks occur in clusters, called bouts, and are episodic or chronic. Common triggers include alcohol, nitroglycerin, food containing nitrates, and strong odors. Abortive treatments include triptans and oxygen; transitional treatments include steroids and suboccipital steroid injections; and prophylactic treatments include verapamil, lithium, melatonin, and topiramate. Newer treatments for cluster headache include galcanezumab, neurostimulation, and somatostatin receptor agonists. (*Am Fam Physician*. 2022;105(1):24-32. Copyright © 2022 American Academy of Family Physicians.)



Illustration by Jennifer Fairman

Cluster headache is the most common form of trigeminal autonomic cephalgia, and it affects less than 1% of the population. It is characterized by attacks of severe unilateral pain located in the orbital, supraorbital, and/or temporal region. This article provides a review of patient-oriented evidence to guide the diagnosis and management of cluster headache.

Epidemiology and Risk Factors

- Typical age of onset is 20 to 40 years^{1,2}; it is two to three times more common in men than women.³
- Lifetime prevalence is 124 per 100,000.⁴

- Having a first-degree relative with cluster headache increases the patient's risk five to 18 times, whereas having a second-degree relative with cluster headache increases the risk one to three times.⁵

Diagnosis

- Cluster headache is a clinical diagnosis based on the criteria described in *Table 1*.²
- Cluster headache patterns are episodic or chronic. Headache episodes that last seven days to one year with remission periods lasting three months or longer are episodic. When episodes last for one year or longer with remission periods of less than three months, they are categorized as chronic.¹
- A suggested approach to the evaluation of acute headache is summarized in *Figure 1*.^{1,2,6}

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis of cluster headache includes other trigeminal autonomic cephalgias

CME This clinical content conforms to AAFP criteria for CME. See CME Quiz on page 15.

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Patient information: A handout on this topic, written by the authors of this article, is available at <https://www.aafp.org/afp/2022/0100/p24-s1.html>.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	Comments
A sense of restlessness is one key feature of cluster headache and should be elicited in the history. ^{1,3}	C	Consensus statement
First-line abortive therapies for cluster headache include 100% supplemental oxygen, subcutaneous sumatriptan (Imitrex), sumatriptan nasal spray, and intranasal zolmitriptan (Zomig). ^{16,19-22,24-26}	A	Good quality meta-analyses and randomized controlled trials
Suboccipital steroid injection may be considered for transitional therapy to provide time for prophylactic therapy to take full effect. ^{14,32,33}	A	Good quality randomized controlled trials
First-line prophylactic therapy for cluster headache is verapamil. ^{12,34,37}	A	Good quality randomized controlled trials

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <https://www.aafp.org/afpsort>.

such as paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms, hemicrania continua, or secondary cluster headache caused by intracranial structural lesions (e.g., pituitary adenoma).^{1,7}

- Trigeminal neuralgia typically affects the second and third branches of the trigeminal nerve, whereas the first branch is affected in cluster headache.^{1,7}

- Migraine headaches are often accompanied by other symptoms that are not typical of cluster headache, including photophobia, phonophobia, and nausea or vomiting. Most patients with migraine find movement worsens their headache, whereas patients with cluster headache can feel agitated and restless.^{1,7}

HISTORY AND PHYSICAL EXAMINATION

- The typical presentation of cluster headache is unilateral severe pain in the orbital, supraorbital, and/or temporal region and is associated with one or more ipsilateral autonomic symptoms, including conjunctival injection, lacrimation, rhinorrhea, nasal congestion, miosis and/or ptosis, eyelid edema, and facial sweating.^{1,7} Another key symptom is a sense of restlessness.^{1,3,7}

- A cluster headache can last from 15 to 180 minutes when untreated and occurs up to eight times per day in a long-term pattern.¹

- Triggers include medications (vasodilators) such as nitroglycerin, histamine release, tobacco exposure, alcohol, foods that contain nitrates, nail varnish, and petroleum.^{1,2}

TABLE 1

Diagnostic Criteria for Cluster Headache

Feature	Criteria
Associated symptoms	At least one ipsilateral symptom in the eye, nose, or face; restlessness or agitation
Duration	15 to 180 minutes*
Frequency	One episode, at least every other day, up to eight episodes per day*
Location	Unilateral orbital, suborbital, and/or temporal
Pain quality	Severe or very severe pain*

Note: At least five episodes are required for a diagnosis. Symptoms cannot be attributed to another condition.

*—Exceptions are allowed if headaches are less severe, and shorter or longer duration in less than one-half of headache attacks.

Adapted with permission from Weaver-Agostoni J. Cluster headache. Am Fam Physician. 2013;88(2):122.

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DIAGNOSTIC TESTING

- Neuroimaging with computed tomography or magnetic resonance imaging is not routinely recommended.
- Imaging should be performed in patients with sudden changes in headache features (e.g., sudden onset, frequency, severity, location, worst headache of the patient's life), presence of neurologic findings (e.g., double vision, blindness, weakness, change in mental status or personality), or systemic illness (e.g., fever, rash).^{1,2,6}

Treatment

Treatment consists of abortive therapy for acute attacks, transitional therapy to provide temporary relief until prophylactic therapy takes effect, and prophylactic therapy for the duration of the episodic cluster or long-term management of chronic cluster headache.^{2,8}

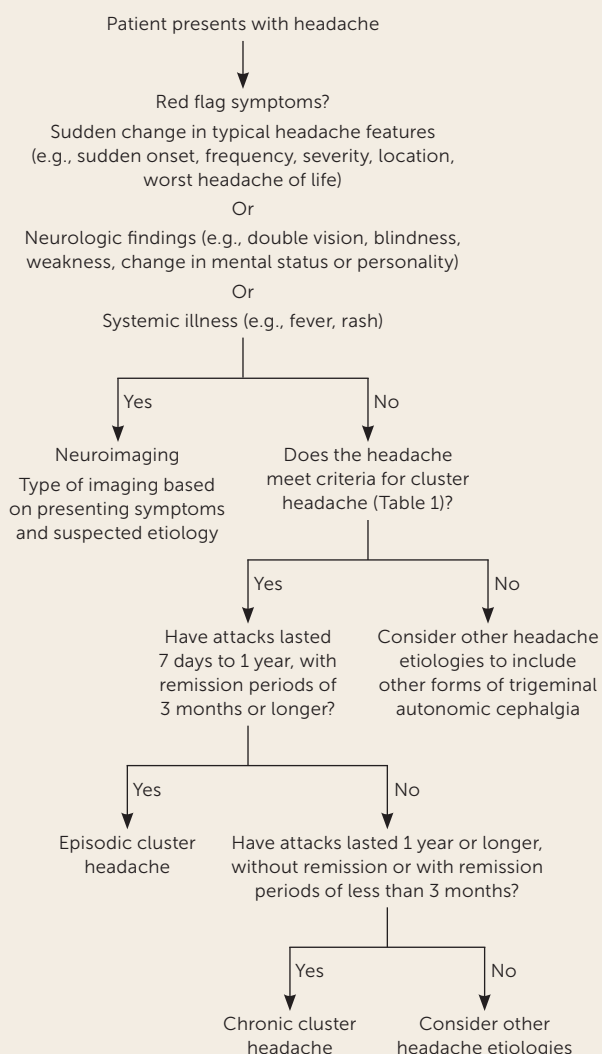
ABORTIVE THERAPY

Abortive therapies for cluster headache are listed in *Table 2*.^{2,8-27}

- First-line therapies include triptan drugs and 100% oxygen.¹⁹
- Subcutaneous sumatriptan (Imitrex), 6 mg, is a first-line treatment option. In two randomized placebo-controlled trials, sumatriptan provided relief as early as 15 minutes after being administered (74% decrease in headache severity in the sumatriptan group vs. 26% in the placebo group).^{2,8,20-22}
- Sumatriptan nasal spray, 20 mg, is considered a first-line option for acute bouts of cluster headache, although it acts slower than subcutaneous sumatriptan.²⁸
- Oral zolmitriptan (Zomig) is considered a second-line treatment option. It is effective only for acute attacks in episodic cluster headache.^{2,8,23}
- Zolmitriptan nasal spray, 5 mg or 10 mg, reduces headache severity at 30 minutes compared with placebo (number needed to treat [NNT] = 2 to 3 for 10 mg; NNT = 5 to 6 for 5 mg) and is considered a first-line therapeutic option.^{2,24,25}
- Adverse effects of triptans include paresthesia; heaviness felt in limbs, chest, head or neck, and other parts of the body; asthenia; nausea; and dizziness.^{8,23}
- Triptans are contraindicated in patients with cardiovascular disease, cerebrovascular disease, and uncontrolled hypertension.¹²

- 100% oxygen is considered first-line therapy for acute cluster headache. One randomized controlled trial found it effective at a flow rate of 12 L per minute for 15 minutes (NNT = 2).^{16,26}
- The U.S. Centers for Medicare and Medicaid Services does not cover home oxygen for cluster headache, but many private health care insurance providers reimburse the cost of oxygen use for this indication.^{9,27}

FIGURE 1



Algorithm for the evaluation of acute headache.

Information from references 1, 2, and 6.

TABLE 2

Abortive Therapy for Cluster Headache

Therapy	Dosing	Adverse effects	Comments	Cost*
Oxygen†	100% via nonrebreather face mask at 12 to 15 L per minute for 15 to 20 minutes	None	Not covered by Medicare or Medicaid except for patients enrolled in studies of oxygen use for cluster headache	< \$1,000 annually for episodic cluster headache patients < \$5,000 annually for chronic cluster headache patients ⁹
Sumatriptan (Imitrex)†	6 mg, subcutaneously; may repeat once at least one hour later 20 mg, nasal spray; maximum of 40 mg per day	Mild to moderate; rarely leads to discontinuation Injections: dizziness, fatigue, injection site reactions, nausea, paresthesia, vomiting Nasal spray: bitter taste	Contraindications include cardiovascular and cerebrovascular disorders and uncontrolled hypertension	Subcutaneous injection: \$15 (\$200) for one vial (6 mg per 0.5 mL) Nasal spray: \$105 (\$510) for six 20-mg doses
Zolmitriptan (Zomig)	5 to 10 mg, nasal spray‡; may be repeated once after two hours 5 mg, orally; maximum of 10 mg per day	Nasal spray: unpleasant taste, nasal cavity discomfort, somnolence Tablets: asthenia, dizziness, heaviness, nausea, chest tightness, paresthesia	Mild adverse effects in approximately 25% to 33% of patients Effective in episodic cluster headache, not in chronic cluster headache	Nasal spray: Not available (\$580) for six 5-mg single-use devices Oral: \$10 (\$385) for three 5-mg tablets
Corticosteroids	Prednisone: 50 to 80 mg of oral prednisone per day, tapered gradually over 10 to 12 days Methylprednisolone: 100 mg orally, or 500 mg intravenously for five days	Hyperglycemia, hypertension, increased appetite, insomnia, nervousness	May be useful for transitional therapy	Prednisone: \$3 for five 50-mg tablets Methylprednisolone: \$10 for 100-mg dose (three 32-mg tablets and one 4-mg tablet) \$50 for one 500-mg intravenous dose ¹⁰
Lidocaine	Nasal: 1 mL of 10% solution applied bilaterally with a cotton swab for five minutes	Nasal congestion, unpleasant taste	Some studies recommend application in the ipsilateral nostril 10% lidocaine, which was evaluated in a randomized controlled trial, ¹¹ is not readily available in the United States 4% lidocaine nasal spray may be compounded	Not available
Octreotide (Sandostatin)	100 mcg per mL subcutaneously ¹²⁻¹⁴	Bloating, diarrhea, dull background headache, injection site reactions, lethargy, nausea	—	\$4 (\$35) per dose
Noninvasive vagal nerve stimulation	Transcutaneous stimulation of the vagus nerve in the neck with three consecutive two-minute stimulations for up to four attacks (eight treatments) per day	Site reaction: burning, tingling, soreness, stinging, skin irritation, redness, erythema, facial neurologic reaction (i.e., drooping and twitching), metallic taste	Approved by the U.S. Food and Drug Administration for abortive and preventive treatment of cluster headache	\$9,510 annually ¹⁵

Note: Treatments are listed in approximate order of use.

*—Estimated lowest GoodRx price for treatment (varies per patient), unless otherwise noted. Actual cost will vary with insurance and by region. Generic price listed first; brand name in parentheses. Information obtained at <https://www.goodrx.com> (accessed September 29, 2021; zip code 66211).

†—First-line agents.

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- Octreotide (Sandostatin), 100 mcg per mL administered subcutaneously, was shown to be superior to placebo (52% decrease in headache severity in the treatment group vs. 36% in the placebo group; NNT = 7) in one double-blind placebo-controlled crossover study. Gastrointestinal upset was the most common adverse effect. Octreotide is not contraindicated in patients with ischemic heart disease.¹³
- Nasal lidocaine may be considered for treatment of acute cluster headache.^{8,11} In a small randomized crossover trial with 15 patients, 1 mL of 10% lidocaine administered nasally via a cotton swab to the area corresponding to the sphenopalatine fossa resulted in a shorter time to headache extinction compared with saline application (37 vs. 59 minutes; $P < .05$).¹¹
- Although intramuscular ergotamine, dihydroergotamine nasal spray, intravenous somatostatin receptor agonists, and oral prednisone have been shown to improve cluster headache response, one systematic review and meta-analysis concluded that there is insufficient evidence to recommend their use because of methodologic limitations of the studies.⁸ In a double-blind placebo-controlled trial, dihydroergotamine nasal spray reduced cluster headache severity compared with placebo (29.9% vs. 9%; NNT = 5).²⁹

TRANSITIONAL THERAPY

- Transitional therapy, such as suboccipital steroid injections and oral or intravenous corticosteroids, should be considered during initiation of prophylactic therapy to provide time for the prophylactic therapy to take full effect.^{12,14,30,31}
- First-line transitional therapy is suboccipital steroid injection.^{32,33}
- Only short-term use of corticosteroids is recommended because of serious adverse effects associated with their use.

PROPHYLACTIC THERAPY

Table 3 summarizes prophylactic therapy options.^{2,8,12,14,15,18,19,32-47}

- Verapamil is considered the first-line agent for cluster headache prophylaxis.^{2,12} A double-blind, parallel-group, randomized controlled trial comparing verapamil, 120 mg three times per day, with placebo found that those given verapamil were more likely to have a decrease of headache frequency by at least one-half (80% vs. 0%).³⁷ Most

experts agree that electrocardiography should be performed before beginning verapamil therapy, but there is no consensus on whether monitoring with electrocardiography should be done with dose changes.³⁴

- Galcanezumab (Emgality) is a monoclonal antibody targeting calcitonin gene-related peptide and is approved by the U.S. Food and Drug Administration for treatment of migraine. It was shown in a randomized trial to decrease headache frequency by at least one-half more often than with placebo during weeks 1 through 3 (71% vs. 53%; $P < .05$; NNT = 5).³⁵ In that study, it was administered subcutaneously once per month as three consecutive injections with a pre-filled syringe of 100 mg per mL. The long-term safety and durability of the drug's benefit require longer studies.¹⁴
- Nasal civamide, 50 mcg, may be modestly effective as prophylaxis for episodic cluster headache, but it is not available in the United States.^{18,38}
- Melatonin, 10 mg per day, may be considered for prevention of cluster headache, particularly in patients who are not able to tolerate other medications.^{8,19,39,40}
- Lithium may be considered if verapamil is contraindicated or not effective.^{12,42}
- Although topiramate (Topamax) has been recommended, there is no evidence from clinical trials.^{12,14}
- Valproate sodium does not appear to be an effective treatment option for cluster headache.^{8,14,39,43}

SURGICAL TREATMENT

- There are several invasive neurostimulation devices intended for the treatment of cluster headache.
- In two randomized controlled trials, sphenopalatine ganglion stimulation decreased the frequency of chronic cluster headache attacks and provided acute relief.^{18,44} In one study, 67.1% of patients who received treatment with sphenopalatine ganglion stimulation achieved pain relief in 15 minutes compared with 7.4% in the sham treatment group (NNT = 2; $P < .0001$).⁴⁴ Further research is needed to establish its role in clinical practice.¹⁸
- There is insufficient evidence of benefit to recommend deep brain stimulation.^{45,46}

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TABLE 3

Prophylactic Therapy for Cluster Headache

Therapy	Dosing	Adverse effects	Comments	Cost*
Verapamil†	Varies; minimum of 240 mg orally per day, in a single or divided dose ² ; no clear consensus on what maximum dose should be	Abdominal discomfort, bradycardia, constipation, edema, gum hyperplasia, hypotension	Electrocardiography is recommended before starting medication, and most experts recommend repeat testing before and after dose changes, although there is no expert consensus on how often ³⁴ Monitor for prolonged PR interval, change in cardiac axis, or broadening of QRS with higher doses	\$6 for 90 80-mg tablets
Lithium	800 to 900 mg, taken with meals in divided daily doses	Hypothyroidism, nephrogenic diabetes insipidus, polyuria, tremor	May be considered if verapamil is contraindicated or not effective	\$5 for 90 300-mg tablets
Topiramate (Topamax)	25 mg orally for seven days, then increase by 25 mg per day every week to at least 100 mg per day and a maximum of 400 mg per day	Dizziness, paresthesia, slow speech; mostly well tolerated	Contraindicated in patients with nephrolithiasis	\$3 (\$500) for 30 100-mg tablets
Galcanezumab (Emgality)	Three subcutaneous injections with a pre-filled syringe of 100 mg per mL monthly	Injection site pain	Longer and larger trials are needed to evaluate the safety and durability of this medication ³⁵	Not available (\$1,700) for three prefilled syringes of 100 mg per mL
Melatonin	10 mg orally at bedtime	None	—	\$1 per 5-mg dose
Noninvasive vagal nerve stimulation	Transcutaneous stimulation of the vagus nerve in the neck with three consecutive two-minute stimulations twice per day ³⁶	Site reaction: burning, tingling, soreness, stinging, skin irritation, redness, erythema, facial neurologic reaction (i.e., drooping and twitching), metallic taste	Approved by the U.S. Food and Drug Administration for abortive and preventive treatment of cluster headache	\$9,510 annually when used as an adjunct to medication ¹⁵
Sphenopalatine ganglion or deep brain stimulation	Surgical implantation	Pain, swelling, hematoma, seroma, vertigo, double vision, localized sensory disturbances	Further studies needed to establish the role of these therapies in clinical practice Deep brain stimulation is not recommended because of associated risks Not yet widely accepted as a primary therapy	Not available (German studies only)

Note: Treatments are listed in approximate order of use.

*— Estimated lowest GoodRx price for one month's treatment, unless otherwise noted. Actual cost will vary with insurance and by region. Generic price listed first; brand name in parentheses. Information obtained at <https://www.goodrx.com> (accessed August 31, 2021; zip code 66211).

†—First-line agents.

Information from references 2, 8, 12, 14, 15, 18, 19, and 32-47.

- Gamma Knife radiotherapy was studied in a prospective, nonblinded, open study, but the morbidity was too great for the low rate of pain cessation even in patients with refractory chronic cluster headache.⁴⁸ In a more recent case series, Gamma Knife radiotherapy decreased cluster headache pain significantly in 60% of treated patients at 34 months' follow-up, but 50% of patients who were irradiated at the trigeminal nerve experienced facial sensory dysfunction.⁴⁹

COMPLEMENTARY MEDICINE

- Tryptamines, primarily psilocybin and lysergic acid diethylamide (LSD), have been reported on social forums to provide abortive and preventive therapy.⁵⁰ Use of these substances is anecdotal, and no clinical trials of these drugs have been completed.
- The effectiveness of cannabis for the treatment of cluster headache is unclear. Cannabis users have reported full symptom relief, some improvement, and exacerbation of symptoms.⁵⁰
- No alternative therapies were found to be consistently effective, including acupuncture, herbal treatment, chiropractic treatment, homeopathy, reflexology, hypnosis, spiritual therapy, massage, aromatherapy, relaxation therapy, physiotherapy, and yoga.⁵¹

OTHER TREATMENTS

- The U.S. Food and Drug Administration has approved noninvasive vagus nerve stimulation for the treatment and prevention of acute episodic and chronic cluster headache. Two randomized controlled trials comparing noninvasive vagus nerve stimulation with sham stimulation found that headache response was significantly improved with nerve stimulation in patients with episodic cluster headache. There was no benefit in patients with chronic cluster headache.^{52,53} A study comparing standard of care alone with standard of care plus noninvasive vagus nerve stimulation found that nerve stimulation led to a significant, quick, sustained decrease in cluster headache frequency two weeks after it was added to standard of care.⁵⁴

Prognosis

- Longitudinal data on cluster headache are anecdotal and suggest that the natural history of the condition is to remit with age.^{51,55,56} However,

in a study of 189 patients with cluster headache who were interviewed during a 10-year period, all patients continued to have cluster headache at the end of the study, although for some their chronic cluster headache evolved into episodic cluster headache and vice versa.⁵⁷

This article updates previous articles on this topic by Weaver-Agostoni² and Beck, et al.⁵⁸

Data Sources: We searched Essential Evidence Plus, PubMed, and Google Scholar. Key words included cluster headache, cluster headache and causes, cluster headache and diagnosis, cluster headache treatment. The search included meta-analyses, randomized controlled trials, and medical society guidelines. Level of evidence and recommendations were derived from the American Headache Society's evidence-based guidelines. The European Federation of Neurologic Societies guidelines were also referenced. Search dates: November 2020 to February 2021 and September 2021.

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