



Cluster Headache

Neurology
Ambassador
Program

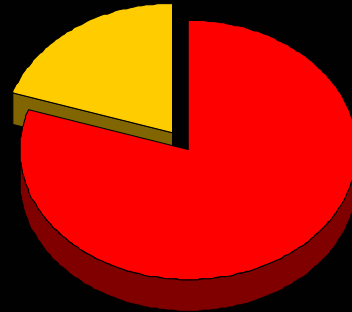
OBJECTIVES

- Describe the clinical features and diagnosis of cluster headache
- Discuss the pathogenesis of cluster pain and autonomic features
- Review acute and preventive therapy
- Overview of new treatment horizons for refractory chronic cluster

IHS CLASSIFICATION

Cluster headache

- Episodic type (80%)
- Chronic type (20%)
(Cluster period lasts for more than one year without remission or remission lasts less than 14 days)



■ Episodic ■ Chronic

IHS Headache Classification Committee. *Cephalalgia*. 2004.

Although the unique clinical features of cluster headache (CH) have been recognized since the 17th century, the striking periodicity was not articulated until the 1940s. The term “cluster headache” was coined in the 1950s, and since then the International Headache Society (IHS) has identified and classified two major temporal patterns of CH (1). The episodic type (ECH), by far the most common (90%), is characterized by discrete attack and remission phases. The chronic type (CCH) is defined by attacks that occur daily for more than one year without remission or with remission periods lasting less than 14 days.

Cluster headache is rare (about 0.4% of the general population), and it predominates in males, although recent studies indicate that the rate in females is rising (2). Onset can occur at any age but usually begins between 30 and 50 years of age (3).

In contrast to migraine headache, genetics in cluster headache is not thought to be important, although recent studies have shown a positive family history in about 7% of patients with cluster headache. When compared with prevalence of CH in the general population, first-degree relatives have about a 14-fold increased risk of developing CH. Furthermore, in one study, five sets of monozygotic twins were 100% concordant for CH (4).

A number of related short-lasting headaches, referred to as “cluster variants,” may be confused with cluster headache. These less common variants include chronic and episodic paroxysmal hemicranias and short-lasting unilateral neuralgiform with conjunctival injection and tearing (or SUNCT). Cluster variants have a number of distinguishing features that have therapeutic implications and are important to recognize. These related syndromes will be reviewed later in this presentation.

1. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders. *Cephalalgia*. 2004;24(suppl 1):1:160.
2. Ekblom K, Ahlborg B, Schele R. Prevalence of migraine and cluster headache in Swedish men of 18. *Headache*. 1978;18(1):9-19.
3. Swanson JW, Yanagihara T, Stang PE, et al. Incidence of cluster headaches: a population-based study in Olmstead County Minnesota. *Neurology*. 1994;44:433-437.
4. Russell MB. Genetic epidemiology of migraine and cluster headache. *Cephalalgia*. 1997;17:683-701.

AGE OF ONSET

- 80% with first attack (2nd-4th decades)
- Mean age of onset 31.5 years (27-37 yrs)
- Range

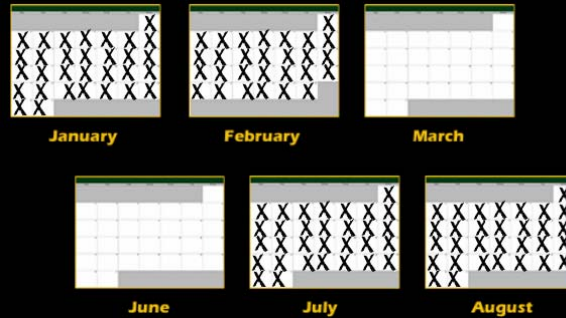
Youngest – 1 yr old

Oldest – 80+ yrs



The onset of migraine occurs between the second and fourth decade, for the majority of sufferers. However, migraine can develop early in life or later in life.

CIRCANNUAL PERIODICITY Cluster Periods



Kudrow L. *Cephalalgia*. 1987.

Waldenlind E. *Cluster Headache and Related Conditions*. 1999.

The most striking feature of CH – the feature from which its name is derived – is the unmistakable periodicity of the attacks. Individual cluster attacks occur during attack phases known as “cluster periods.” Most patients have one or two annual cluster periods, each lasting between one and three months. Some patients have a seasonal propensity for attacks related to the duration of the photoperiod, with the highest incidence of attacks occurring in January or July. Intriguingly, the attacks occur soon after the shortest and longest days of the year. This may have pathophysiologic implications, which we will discuss later.(1)

Kudrow demonstrated that the most likely times for a cluster period to begin were associated with the number of daylight hours; that is, more exacerbations occur within two weeks following the summer and winter solstices, with fewer exacerbations beginning within two weeks of the onset and offset of daylight savings time.(2)

Cluster periods punctuate longer-lasting remission periods, which usually last six months to two years. During remission periods, neither spontaneous nor provoked attacks occur. Although the duration of cluster and remission periods varies among individuals, these periods remain relatively consistent within the same individual.

1. Waldenlind E. Biological rhythm in cluster headache. In: Olesen J, Goadsby PJ, eds. *Cluster Headache and Related Conditions*. London, England: Oxford University Press;1999:171-178.
2. Kudrow L. The cyclic relationship of natural illumination to cluster period frequency. *Cephalalgia*. 1987;7 (Suppl 6):76-77.

CIRCADIAN PERIODICITY Cluster Attacks

1 to 3 attacks daily (up to 8 attacks/day)

Peak time periods



REM sleep;
Obstructive sleep apnea

Chervin RD et al. *Neurology*. 2001, Trucco M, Waldenlind E. *Cephalalgia*. 1993.

Cluster headache also has a striking circadian periodicity, with most individuals having one to three attacks per day, although some have up to eight attacks daily. In an individual patient, the attacks usually occur at the same time each day. As shown on this illustration, the most common times for cluster attack onset are 1 a.m. to 2 a.m., 1 p.m. to 3 p.m., and 9 p.m.

In addition, cluster headache is characterized by nocturnal attacks that generally occur around the same time each night, with a peak incidence between 1 a.m. and 3 a.m., as seen here in this first clock. This time roughly correlates with the onset of the first period of rapid eye movement (REM) sleep. Although this relationship has been well documented, the significance and exact relationship of this association remains unclear.

There appears to be a relationship in some patients of cluster headache and obstructive sleep apnea (OSA). One possible trigger for cluster headache attacks may be the observed hypoxia or hypercapnia normally associated with OSA.

Chervin RD, Zallek SN, Lin X, Hall JM, Sharma N, Hedger KM. Sleep disorder breathing in patients with cluster headache. *Neurology*. 2000;54(12):2302-2306.

Trucco M, Waldenlind E. Circadian distribution of episodic cluster headache attacks. *Cephalalgia*. 1993;13 (Suppl 13):196.

ATTACK PROFILE

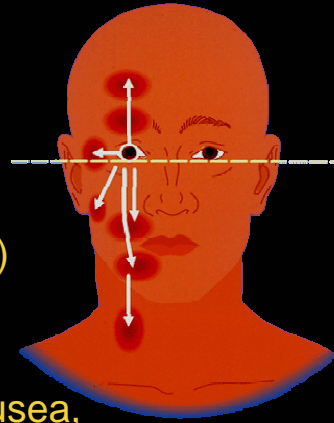
Unilateral orbital / temporal severe pain

Rapid onset (5 – 15 min)
Short duration (45 – 90 min)

Agitation/restlessness (90%)

Autonomic features

“Migrainous” symptoms: nausea, photophobia, phonophobia, aura



Campbell JK: *Seminars in Neurology*, 1988

As distinctive as its periodicity, each individual cluster attack has a highly stereotyped profile. The attacks are almost exclusively unilateral, and the pain is excruciatingly severe, located mainly around the orbit and temporal region. Most patients suffer from strictly unilateral attacks, although the headache may alternate sides between cluster periods or, more rarely, within the same cluster period. The headache peaks within minutes and usually lasts between 45 and 90 minutes, although some last up to 8 hours. In contrast to the quiescent state seen in migraine, the cluster patient prefers to pace in an agitated and colicky state, where neither position nor rest offers any relief.

Over the past few years, several authors have reported in independent studies that migrainous symptoms, such as prodromal and premonitory symptoms, nausea, vomiting, photophobia, phonophobia, and even visual aura, are more commonly associated with cluster attacks than was previously recognized. Whether this reflects a shared underlying pathogenesis or a similar phenotype based on a common final pathway for expression is unclear.

Cranial autonomic symptoms occur in the vast majority of patients and are considered integral to the diagnosis of this syndrome.

Campbell JL. Facial pain due to migraine and cluster headache. *Semin Neurol*. 1988;8(4):324-331.

Dodick DW, Campbell JK. Cluster headache: diagnosis, management and treatment. In: Silberstein SD, Lipton RB, Dalessio DJ, eds. *Wolff's Headache And Other Head Pain*. 7th ed. New York, NY: Oxford University Press; 2001:283-309.

CRANIAL AUTONOMIC SYMPTOMS

- Lacrimation (90%)
- Conjunctival injection (75%)
- Nasal stuffiness, rhinorrhea (75%)
- Ptosis, eyelid edema (75%)



Autonomic symptoms are present in more than 97% of patients. Among the local signs of autonomic involvement, lacrimation and conjunctival injection are the most common, each present in more than 80% of patients. Nasal stuffiness or rhinorrhea is experienced by 70% to 75% of sufferers. All autonomic symptoms are transient, lasting only for the duration of the attack, with the exception of a partial Horner's syndrome, which occurs in up to 66% of cases and may become persistent after long periods of attacks. On occasion, a patient may notice some degree of facial flushing, sweating or edema.

Dodick DW, Campbell JK. Cluster headache: diagnosis, management and treatment. In: Silberstein SD, Lipton RB, Dalessio DJ, eds. *Wolff's Headache And Other Head Pain*. 7th ed. New York, NY: Oxford University Press;2001:283-309.

DISTINGUISHING CLUSTER FROM OTHER TRIGEMINAL AUTONOMIC CEPHALGIAS

Feature	Cluster	PH	SUNCT	HC
Sex (M:F)	3:1	1:3	3:1	1:2
Attack duration	60 min	15 min	5-250 s	mins-days
Attack frequency	1-3/day	≥ 5/day	1/day-30/hr	variable
Autonomic features	+	+	+	+
Indocin effect	+/-	+	-	+

SUNCT = short-lasting unilateral neuralgiform pain with conjunctival injection and tearing syndrome; PH = paroxysmal hemicrania; HC = hemicrania continua

Goadsby PJ, Lipton RB. *Brain*. 1997.

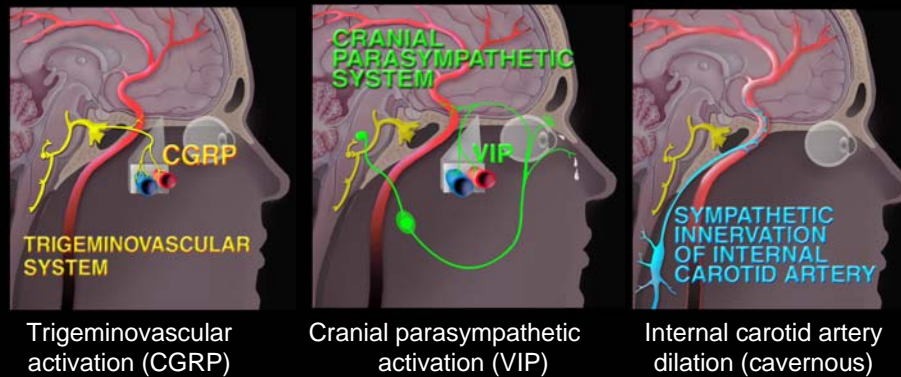
This slide compares the features of cluster headache, paroxysmal hemicrania (PH), short-lasting unilateral neuralgiform pain with short-lasting unilateral neuralgiform with conjunctival injection and tearing (SUNCT), and hemicrania continua (HC). A number of primary headache syndromes, characterized by discrete, short-lasting, episodic attacks of intense unilateral orbital-temporal headache and robust autonomic signs, are difficult to distinguish from cluster headache in clinical practice. Because of the trigeminal distribution of the pain and the ipsilateral autonomic symptoms, these headache syndromes as a group have been referred to as trigeminal autonomic cephalgias. These related syndromes, like cluster headache, often occur during sleep and may be precipitated by alcohol.

As shown on this chart, only cluster headache and SUNCT occur predominately in males. In a few cases, lamotrigine, topiramate, and gabapentin may be effective in the treatment of SUNCT.

Chronic paroxysmal hemicrania and episodic paroxysmal hemicrania and SUNCT differ from cluster headache in their higher frequency and shorter duration of individual attacks with an almost inverse relationship of these events. In other words, as the attack frequency increases, attack duration tends to decrease. The distinction between these disorders is important because of the differential response to therapy, particularly with respect to the paroxysmal hemicranias, which respond dramatically to indomethacin.

Goadsby PJ, Lipton RB. A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic feature, including new cases. *Brain*. 1997;120:193-209.

PATHOGENESIS OF PAIN: AUTONOMIC SIGNS



Edvinsson L, Goadsby PJ. *Eur J Neurol*. 1998.

Although a unifying pathophysiologic explanation of cluster headache is not yet available, any attempt to understand this syndrome must take into account the three cardinal features of the disorder. These include pain, autonomic features, and stereotyped periodicity.

Seminal observations on the neurobiology of cluster headache have recently been made. To recognize their significance, a basic understanding of neurovascular anatomy is essential.

First, cephalic pain is relayed to the central nervous system via nociceptive ophthalmic branches of the trigeminal nerve, which innervates pain-sensitive intracranial structures such as the dura mater and dural blood vessels. Substance P and calcitonin gene-related peptide (CGRP) are trigeminovascular neuropeptides that are released in both animals and humans when the trigeminal fibers or ganglion are activated. CGRP, the most potent vasodilator in the human body and in animal models, when released, leads to the production of neurogenic inflammation and dilation of dural blood vessels. Activation of the trigeminovascular system in cluster headache has been corroborated by recent evidence demonstrating markedly elevated blood levels of CGRP in the external jugular vein (EJV) of patients during a cluster attack.

Second, the autonomic features of CH indicate activation of the cranial parasympathetic fibers. These fibers originate from first-order neurons within the superior salivatory nucleus, which has a functional brainstem connection to the trigeminal nucleus caudalis. These fibers travel with the seventh cranial nerve and synapse in the pterygopalatine ganglia. Post-ganglionic fibers provide vasomotor and secretomotor innervation to the cerebral blood vessels and the lacrimal and nasal mucosal glands, respectively. Activation of this pathway has similarly been supported by the finding of dramatically elevated blood levels of vasoactive intestinal polypeptide (VIP) in the EJV of sufferers during an attack.

The presence of a postganglionic Horner's syndrome during attacks of CH indicates involvement of the carotid sympathetic plexus. The cavernous carotid artery is a likely location since it is at this level where the parasympathetic, sympathetic, and trigeminal fibers converge. Indeed, evidence from a variety of imaging sources has demonstrated the presence of arterial dilatation and venous outflow obstruction in the region of the cavernous sinus. This evidence collectively provides an explanation for the pain and autonomic features underlying a cluster attack, but does not account for the periodicity of the syndrome.

Edvinsson L, Goadsby PJ. Neuropeptides in headache. *Eur J Neurol*. 1998;5:329-341.

PERIODICITY: THE RESULT OF DYSFUNCTIONAL HYPOTHALAMUS

- Altered secretory circadian rhythms of hypophyseal hormone systems (melatonin, testosterone, beta-endorphin, beta-lipotropin, cortisol, prolactin)

- Circannual and circadian rhythmicity

- Seasonal predilection of cluster periods



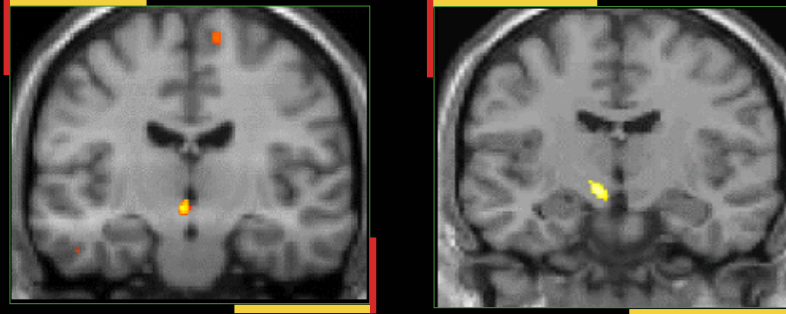
Leone M, Bussone G. *Cephalalgia*. 1993.

Peripheral neurovascular structure involvement can explain the pain and autonomic signs of cluster headache, but not its rhythmicity. The remarkable circadian, circannual, and seasonal rhythmicity of cluster headache suggests a periodic disturbance of hypothalamic activity.

Over a period of twenty years, studies have found abnormal pituitary hormone levels during cluster periods, indicating altered secretory hypothalamic rhythms in these patients. Most of these rhythms returned to normal during periods of cluster headache remission. Hormonal abnormalities in cluster headache are associated with disorders of hypothalamic function.

Leone M, Bussone G. A review of hormonal findings in cluster headache. Evidence for hypothalamic involvement. *Cephalalgia*. 1993;13:309-317.

HYPOTHALAMIC DYSFUNCTION- CLUSTER AND SUNCT



H-Spectroscopy demonstrates decreased NAA/Cr ratio
In ipsilateral posterior hypothalamus suggesting
neuronal loss/dysfunction

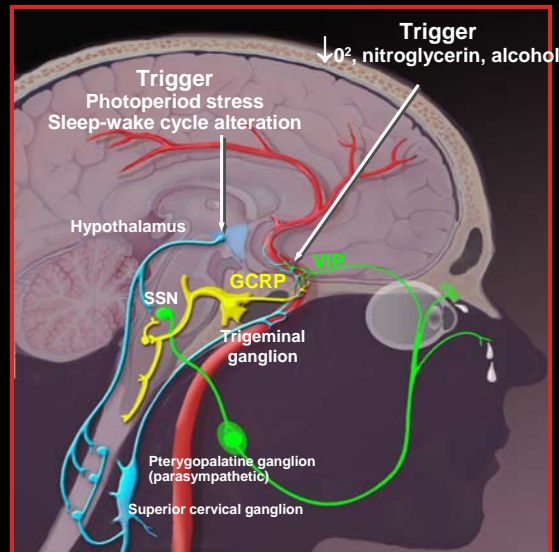
May A et al. *Lancet*. 1998; *Nat Med*. 1999; *Neurology*. 2000.; Lodi R *Cephalalgia* 2003

One study of 9 patients with chronic cluster headache used PET imaging during acute nitroglycerin-induced cluster headache attacks and found marked activation in the hypothalamic grey, an area specific for cluster headache. This activation pattern has not been observed in migraine or experimental ophthalmic division head pain. Furthermore, hypothalamic activation was not seen in the control group of cluster patients given nitroglycerin to induce an attack while they were in remission. This finding implies that the hypothalamus is involved in the pain process in a permissive or triggering manner, rather than simply as a response to first division nociception. Furthermore, given that this area is involved in circadian rhythms and sleep-wake cycling, these data established an involvement of the hypothalamic area in the genesis of an acute cluster attack (1).

Another study that also supports the idea of involvement of the hypothalamic area in CH pathogenesis provides for the first-time tantalizing evidence that primary headache disorders may be associated with abnormal brain *structure* as well as function.(2) Voxel-based morphometric MR imaging, an objective and automated method of analyzing changes in brain structure, was used to study the brain structure of patients with cluster headache. A significant structural difference was found in the hypothalamic gray compared with controls. This structural anomaly correlated with the area of activation demonstrated in the PET studies (2).

1. May A, Bahra A, Buchel C, et al. Hypothalamic activation in cluster headache attacks. *Lancet*. 1998;352:275-278.
2. May A, Ashburner J, Buchel C, et al. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. *Nat Med*. 1999;5(7):836-838.
3. May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ. PET and MRA findings in cluster headache and MRA in experimental pain. *Neurology*. 2000;55(9):1328-1335.
4. Lodi R, Pierangeli G, Tonon C, et al. Proton MR spectroscopy study of hypothalamus metabolism in patients with cluster. *Cephalalgia* 2003;23(7):656.

CLUSTER HEADACHE PATHOGENESIS



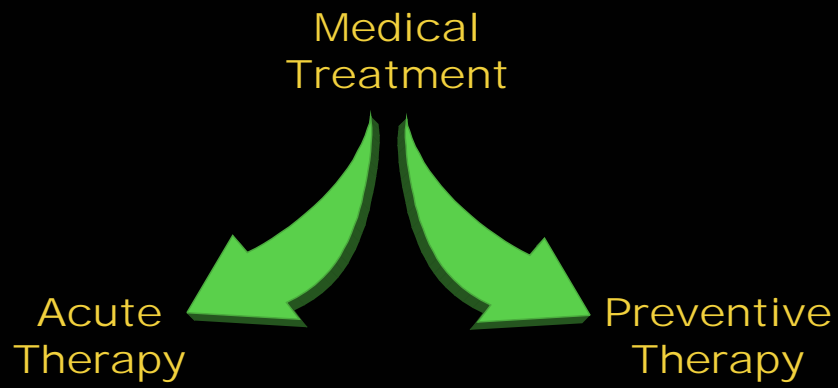
We can envision a model whereby there is dual activation of the trigeminovascular and cranial parasympathetic systems from central- or peripherally-acting triggers at a permissive time, known as the “cluster period”, which is determined by a dysfunctional hypothalamic pacemaker.

Whether or not the hypothalamus actively participates in this process is unclear. The anatomic substrate is clearly present, since the hypothalamus has well-recognized functional connections to the salivatory and other parasympathetic nuclei, as well as to the preganglionic sympathetic neurons within the brainstem and spinal cord.

The activation of these pathways may lead to painful vascular changes within the cavernous sinus, secondary involvement of the sympathetic plexus overlying the cavernous carotid artery, and stimulation of secretory function of the lacrimal and other mucosal glands.

Dodick DW, Campbell JK. Cluster headache: diagnosis, management and treatment. In: Silberstein SD, Lipton RB, Dalessio DJ, eds. *Wolff's Headache And Other Head Pain*. 7th ed. New York, NY: Oxford University Press; 2001:283-309.

TREATMENT



The medical management of CH must include both acute therapy designed to abort individual attacks, as well as prophylactic therapy designed to prevent the recurrent attacks that occur daily during the cluster period.

ACUTE TREATMENT

High efficacy

- O₂
- Sumatriptan subcutaneous (6 mg)
- Sumatriptan nasal spray (20 mg)
- Zolmitriptan (10 mg oral)
- IV/IM/SC dihydroergotamine mesylate 0.5mg – 1.0 mg
- Octreotide subcutaneous (100 mg)

Limited efficacy

- Ergotamine 1 mg – 2 mg oral or suppository
- DHE nasal spray
- Intranasal lidocaine

Bahra A et al. *Neurology*. 2000; Ekbom K et al. *Cephalalgia*. 1995

Although a number of agents may be beneficial for acute therapy, oxygen, sumatriptan, and DHE are highlighted (and detailed in the following slides) because of their consistent efficacy and the speed with which relief is obtained. This is an important consideration in a disorder where the headache peaks quickly and lasts only 45-90 minutes.

A double-blind controlled trial compared the efficacy of 5 mg and 10 mg oral zolmitriptan with placebo for treating acute cluster attacks. Thirty minutes after dosing, 60% of patients receiving zolmitriptan had mild or no pain compared with 42% of placebo-treated patients. Oral or rectal ergotamine and intranasal lidocaine are generally too slow in onset to provide meaningful relief in a timely manner (1,2).

A recent open pilot study investigated the efficacy and tolerability of 20 mg sumatriptan nasal spray in acute treatment of cluster attacks. Among the eight study patients, the overall efficacy was ranked as “excellent” in two, “good” in four, “reasonable” in two and “poor” in two patients. The study concluded that 20 mg sumatriptan nasal spray might be an alternative therapy for acute treatment of cluster headache but double-blind studies were needed to further evaluate efficacy (3).

The next two slides will focus on a review of the efficacy of two of the agents listed here– oxygen and sumatriptan.

1. Bahra A, Gawel MJ, Hardebo JE, Millson D, Breen SA, Goadsby PJ. Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology*. 2000;54(9):1832-1839.
2. Ekbom K, Krabbe A, Micieli G, et al. For the Sumatriptan Cluster Headache Long-term Study Group. Cluster headache attacks treated for up to three months with subcutaneous sumatriptan (6 mg). *Cephalalgia*. 1995;15:230-236.
3. Schuh-Hofer S, Reuter U, Kinze S, et al. Treatment of acute cluster headache with 20 mg sumatriptan nasal spray – an open pilot study. *J Neurol*. 2002;249(1):94-99.
4. 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.

OXYGEN

- 100% O₂ : 7 – 10 liters / min for 15 to 20 minutes
- Efficacy 70% at 15 minutes
- Most effective when headache is at maximum intensity
- May delay rather than abort attack
- Main limitation is lack of accessibility and inconvenience

Fogan L. *Arch Neurol.* 1985.

Oxygen is effective in about 70% of patients within fifteen minutes. Oxygen may be most effective in some patients if administered when the headache is at maximum intensity. Unfortunately, in some patients, oxygen seems to delay the attack rather than abort it completely.

The standard treatment for acute cluster attacks is inhalation of 100% O₂, delivered at a rate of 7 liters/min for 15 to 20 minutes with a loosely applied face mask. The patient should be sitting forward with hands on knees and facing the floor so as to promote venous drainage.

Although portable regulators are available, the main drawbacks of oxygen therapy for cluster are the inconvenience, lack of accessibility, and the impracticality of having the regulator and canister available at all times.(1,2)

1. Kudrow L. *Cluster Headache: Mechanisms and Management*. New York, NY: Oxford University Press; 1980.
2. Fogan L. Treatment of cluster headache: a double-blind comparison of oxygen vs air inhalation. *Arch Neurol.* 1985;42:362-363.

OXYGEN INHALATION FOR EPISODIC AND CHRONIC CLUSTER

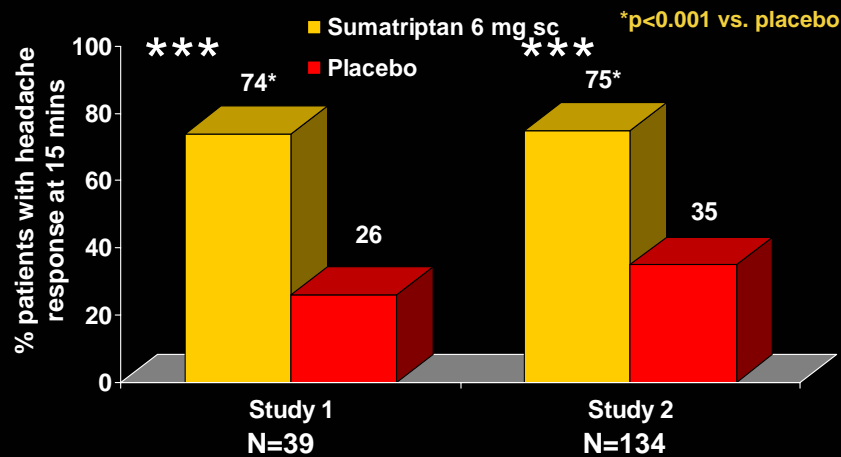
Sex and type of cluster	N	Benefited	
		N	%
Males			
Episodic	26	21	80.8
Chronic	19	13	68.4
Subtotal	45	34	75.6
Females			
Episodic	7	5	71.4
Chronic	0	0	0
Subtotal	7	5	71.4
Total	52	39	75.0

Kudrow L. *Headache*. 1981.

Kudrow reported the results from a study that assessed the benefit of oxygen on patients with episodic or chronic cluster. The majority of the patients were male, and both male and female patients responded to oxygen therapy. There was no apparent difference between chronic and episodic migraine with regard to response to oxygen therapy. Overall, approximately 75% of this group of cluster patients reported benefit from oxygen therapy.

Kudrow L. Response of cluster headache attacks to oxygen inhalation. *Headache*. 1981;21(1):1-4.

15-MINUTE RESPONSE HEADACHE- SUMATRIPTAN SC (6 MG) VS PLACEBO



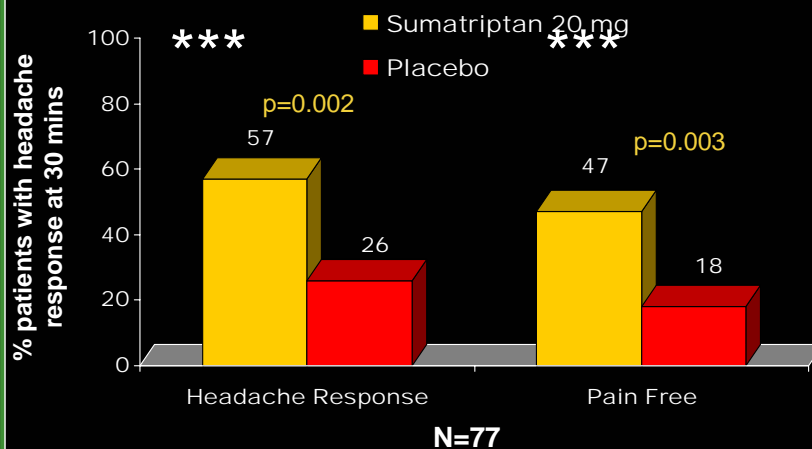
The Sumatriptan Cluster Headache Study Group. *N Eng J Med.* 1991
 Ekbom K et al. *Acta Neurol Scand.* 1993.

In Study 1, among the study group of 39 patients (those who had two cluster attacks and were available for full evaluation), headache severity decreased in 74% of the attacks within 15 minutes of treatment with 6.0 mg subcutaneous sumatriptan as compared with 26% of the attacks for which placebo was given ($P < 0.001$). Thirty-six per cent of the patients were free of pain within 10 minutes after administration of sumatriptan, compared with 3% after placebo. This study concluded that sumatriptan is an effective and well-tolerated treatment for acute attacks of cluster headache (1).

In Study 2, among 134 inpatients with cluster headache, headache relief at 15 minutes after injection was reported by the following: 35% (placebo), 75% (6 mg sc sumatriptan), and 80% (12 mg sc sumatriptan). The 12-mg dose was not significantly better than the 6-mg dose and was associated with more adverse events. The 6-mg dose was recommended for treatment of cluster headache (2,3).

1. The Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. [Abstract] *N Engl J Med.* 1991;325:322-326.
2. Ekbom K, Monstad, I, Prusinski A, et al. Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. The Sumatriptan Cluster Headache Study Group. *Acta Neurol Scand.* 1993;88(1):63-69.
3. Ekbom K, Krabbe A, Micieli G, et al. For the Sumatriptan Cluster Headache Long-term Study Group. Cluster headache attacks treated for up to three months with subcutaneous sumatriptan (6mg). *Cephalalgia.* 1995;15:230-236.

30-MIN RESPONSE HEADACHE- SUMATRIPTAN NASAL SPRAY (20 MG) VS PLACEBO



Van Vliet JA et al. *Neurology*. 2003.

In a double-blind placebo-controlled randomized trial, patients with episodic or chronic cluster headache treated one attack with 20 mg sumatriptan nasal spray and then treated a second attack at least 24 hours later, with matching placebo. Headache scores were rated on a 5-point scale (very severe, severe, moderate, mild, or none) at 5, 10, 15, 20, and 30 minutes. Overall, 5 centers enrolled 118 patients who treated 154 cluster attacks: 77 with sumatriptan and 77 with placebo.

At 30 minutes following treatment, 57% of attacks treated with sumatriptan and 26% treated with placebo achieved a headache response ($p = 0.002$). Thirty-minute Pain-free rates were 47% for sumatriptan and 18% for placebo ($p = 0.003$). Sumatriptan was also more efficacious than placebo in achieving meaningful relief, and relief of associated symptoms. There were no serious adverse events reported for either treatment group.

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.

SUMATRIPTAN SUBCUTANEOUS

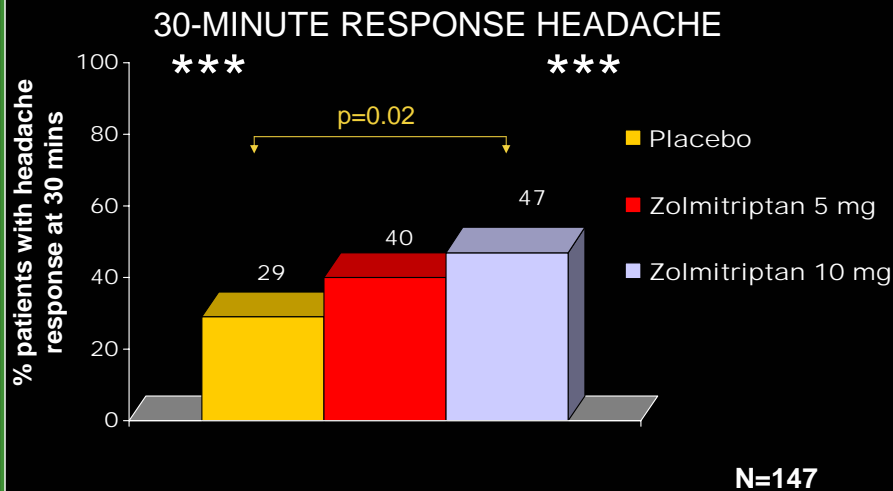
- No tachyphylaxis with repeated use
- Attack frequency not increased with prolonged use
- Not effective for preemptive or preventive treatment
- Overall and median time to pain relief longer in patient with chronic cluster headache

Gobel H et al. *Neurology*. 1998; Ekbom K et al. *Cephalalgia*. 1995.

Sumatriptan, given as a 6-mg SC injection, is effective when given as a self-administered medication for acute cluster attacks. Sumatriptan 6 mg SC has a very rapid and high rate of response and there is no reported evidence for tachyphylaxis or rebound in this group of patients, even with frequent and repetitive use. It is important to note that preemptive treatment prior to the anticipated onset of an attack does not prevent the attack and, therefore, the drug is not used for cluster prophylaxis (1,2).

1. Gobel H, Lindner V, Heinze A, et al. Acute therapy for cluster headache with sumatriptan: findings of a one-year long-term study. *Neurology*. 1998;51:908-911.
2. Ekbom K, Krabbe A, Micelli G, et al. For the Sumatriptan Cluster Headache Long-term Study Group. Cluster headache attacks treated for up to three months with subcutaneous sumatriptan (6 mg). *Cephalalgia*. 1995;15:230-236.

ZOLMITRIPTAN ORAL TABLET (10 MG) VS PLACEBO IN EPISODIC CLUSTER



Bahra A et al. *Neurology*. 2000.

This was a multicenter, double-blind, randomized, three-period, crossover, outpatient study that tested the efficacy of zolmitriptan 5 mg, 10 mg and placebo for the treatment of cluster headache. Adult patients were eligible if they had episodic or chronic cluster headache. Patients only treated moderate to very severe headaches.

Subjects (n=147) patients took at least one dose of study medication. Seventy three percent of the participants were diagnosed with episodic and 27% chronic cluster headache. There was a treatment-by-cluster-headache-type interaction ($p = 0.0453$), so the results were assessed separately for chronic and episodic cluster headache. In patients with episodic cluster headache, the difference between zolmitriptan 10 mg and placebo at 30 minutes reached significance (47% versus 29%; $p = 0.02$; assessed using a 2-point drop in the 5-point cluster scale). Additionally, mild or no pain at 30 minutes was reported by 60%, 57%, and 42% patients treated with zolmitriptan 10 mg, zolmitriptan 5 mg, and placebo (both $p \leq 0.01$ versus placebo).

Bahra A, Gawel MJ, Hardebo JE, Millson D, Breen SA, Goadsby PJ. Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology*. 2000;54(9):1832-1839.

CLUSTER HEADACHE PREVENTION

Transitional

- **Prednisone**
(60 mg daily for 3 days, then 10 mg decrements every 3 days)
- **Ergotamine tartrate**
(1 mg to 2 mg po/ suppository daily)
- **DHE 45**
(0.5 mg to 1 mg sc/ im q 8 – 12 hrs)
- **Occipital Nerve Block ****

Maintenance

- **Verapamil ****
(240 mg to 720 mg/day)
- **Methysergide**
(2 mg tid; up to 12 mg daily)
- **Lithium carbonate**
(150 mg to 300 mg tid)

****Class-I evidence available**

Dodick DW et al. *Cephalalgia*. 2000.

The importance of an effective preventive regimen in patients with CH cannot be overemphasized, since these patients often suffer from one or more attacks on a daily basis, for a period of weeks to months. The goals of preventive therapy are to induce rapid suppression of attacks and to maintain that suppression over the expected duration of a cluster period.

Therefore, preventative treatment in CH is best thought of in terms of transitional and maintenance cluster prophylaxis. Transitional prophylaxis involves the short-term use of either ergotamine, corticosteroids, or DHE, which will usually induce rapid suppression of attacks during the interval of time it usually takes for one of these maintenance drugs to become effective. The use of drugs should be of limited duration, but most patients tolerate them for 3 to 4 weeks.

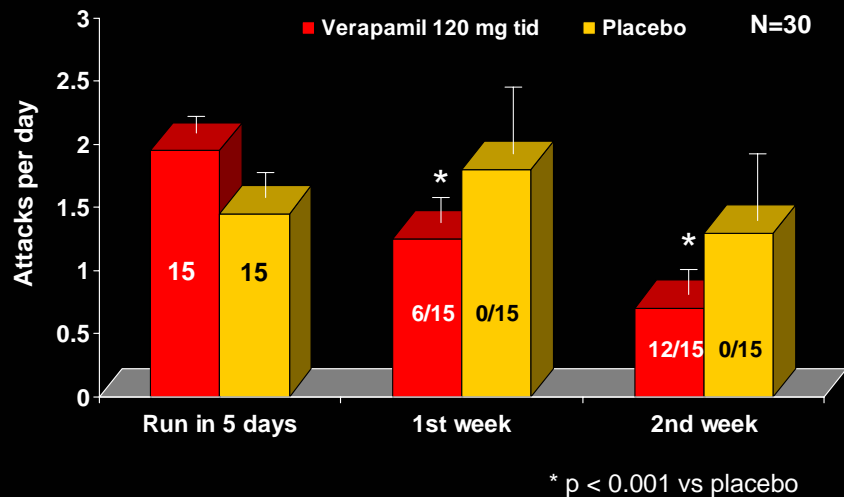
Verapamil can be used as concomitant therapy with one of these quick-acting medications since it has a favorable side-effect profile and does not limit the use or safety of concomitant use of acute sumatriptan, which may be an issue with methysergide or lithium. For the same reason, corticosteroids are preferred over ergotamine or DHE as a transitional prophylactic agent.

An occipital nerve block on the ipsilateral side may be useful as a transitional measure in some patients for temporary relief when the use of other medications may be poorly tolerated or contraindicated.

Methysergide, lithium, and divalproex are effective, for both episodic and chronic cluster. A combination of one or more of these maintenance agents is sometimes used in recalcitrant cases of chronic cluster.

1. Dodick DW, Rozen TD, Goadsby PJ, Silberstein SD. Cluster headache. *Cephalalgia*. 2000;20(9):787-803.
2. Silberstein SD, Peres ME. Hemicrania continua. *Arch Neurol*. 2002;59(6):1029-1030.

VERAPAMIL FOR EPISODIC CLUSTER HEADACHE



Leone M et al. *Neurology*. 2000.

In open-label studies, verapamil has been demonstrated to be effective for the prophylaxis of episodic cluster headache in approximately 75% of patients. Until this study by Leone, there was little controlled evidence of its efficacy in this group of patients.

The authors performed a double-blind, double-dummy study to compare the efficacy of verapamil with placebo in the prophylaxis of episodic cluster headache. After a 5-day run-in period, 15 patients received verapamil (120 mg tid) and 15 received placebo (tid) for 14 days. The authors found a significant reduction in attack frequency and use of abortive agents in the verapamil group. Side effects were mild. These findings provide objective evidence for the effectiveness of verapamil in episodic cluster headache prophylaxis.

Leone M, D'Amico D, Fediani F, et al. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology*. 2000;54(6):1382-1385.

CLUSTER HEADACHE OTHER PREVENTIVE OPTIONS

- Melatonin (10 mg HS)
- Topiramate (50 mg to 200 mg/day)
- Gabapentin (900 mg to 2400 mg/day)
- Divalproex sodium (500 mg to 3000 mg/day)
- Occipital Nerve Block (92% response rate - > 50% reduction in attack frequency; 70% remission Rate by 4 weeks)

Leandri M et al. *Cephalalgia*. 2001; Leone M et al. *Cephalalgia*. 1996; Wheeler SD, Carrazana EJ. *Cephalalgia*. 2000.; Ambrosini A et al. *Cephalalgia*. 2003.

In those patients for whom conventional, first-line drugs are contraindicated, not tolerated, or ineffective, one of these adjunct therapies may be considered.

A small double-blind, placebo-controlled study in twenty intractable, episodic, and chronic cluster patients demonstrated that oral melatonin provided complete relief in about 50% of attacks. Because of its soporific effect and relative lack of side effects, one may decide to use this in combination with other, more conventional agents for the chance of an added benefit (1).

An open-label study demonstrated a high degree of efficacy for topiramate in patients with intractable episodic and chronic cluster headache (2).

Although indomethacin is highly efficacious for some of the trigeminal autonomic cephalalgias (TACs), evidence for its efficacy in CH is limited. Indomethacin may provide added benefit when used in patients who do not respond to a single agent.

Encouraged by results of gabaergic drugs, such as valproate and topiramate, a pilot study was conducted that included 8 patients with episodic cluster headache and 4 with chronic cluster headache, all of whom had not responded to traditional prophylactic drugs. Measuring the number of daily attacks, all patients were pain free after up to 8 days of gabapentin 900 mg given daily. Bouts of headache were reduced to 16% to 40% of the total previously experienced. The investigators hypothesize that the gabaergic action of gabapentin, perhaps combined with other mechanisms, such as calcium channel blockade, may be responsible for the remarkable effects on cluster headache (3).

Another study investigated the prophylactic effect of sodium valproate in cluster headache. In this study, 15 patients had cluster headache (two had the chronic and 13 had the episodic type). The dose used was between 600 mg and 2000 mg per day in 2 doses. Eleven of the 15 patients (73.3%) reacted favorably to the treatment. Sodium valproate appears to be an effective drug in treating cluster headache, but more double-blind, controlled studies are needed (4).

1. Leone M, D'Amico D, Moschiano F, et al. Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. *Cephalalgia*. 1996;16:494-496.
2. Wheeler SD, Carrazana EJ. Topiramate-treated cluster headache. *Neurology*. 1999;53:234-236.
3. Leandri M, Luzzani M, Cruccu G, et al. Drug-resistant headache responding to gabapentin: a pilot study. *Cephalalgia*. 2001;21(7):744-746.
4. Hering R, Kuritzky A. Sodium valproate in the treatment of cluster headache: an open clinical trial. *Cephalalgia*. 1989;9(3):195-198.
5. Ambrosini A, Vandenheede M, Rossi P, et al. Suboccipital (GON) injection with long-acting steroids in cluster headache: a double-blind placebo-controlled study. *Cephalalgia* 2003;23(7):734.

REFRACTORY CLUSTER HEADACHE

- Combination therapy

- Hospitalization / headache specialist
(repetitive IV DHE; IV methylprednisolone)

- Surgery

Dodick DW, Campbell JK. *Wolff's Headache And Other Head Pain*. 2001.

Treatment of chronic cluster headache should be initiated with high-dose monotherapy of any of the preventive options listed. Drug combinations may be necessary in this difficult-to-treat population of patients, but this strategy is not commonly successful or feasible over the long-term because of the inevitability of break-through attacks and the cumulative toxicity associated with drug combinations.

In many cases, these patients should be referred to a tertiary care center with headache expertise. Some patients benefit from a brief hospitalization with aggressive inpatient therapy, usually with repetitive DHE, used in a similar fashion as in patients with intractable migraine. This technique has been shown to be very effective in patients with both episodic and chronic cluster headache.

In a small number of patients who remain resistant to aggressive medical therapy, or when contraindications or intolerable side effects prevail, surgery may be a viable option.

Dodick DW, Campbell JK. Cluster headache: diagnosis, management and treatment. In: Silberstein SD, Lipton RB, Dalessio DJ, eds. *Wolff's Headache And Other Head Pain*. 7th ed. New York, NY: Oxford University Press; 2001:283-309.

INDICATIONS FOR SURGERY

- Medically intractable

- Contraindications or intolerable side effects to medications

- Strictly unilateral cases

- Stable psychological and personality profiles including low addiction proneness

Dodick DW, Campbell JK. *Wolff's Headache And Other Head Pain*. 2001.

Only those patients with stable psychological profiles who are truly medically intractable, and whose attacks have remained exclusively unilateral, are considered surgical candidates. Patients who have had attacks that alternated sides are at an increased risk of developing postoperative recurrence on the opposite side.

Dodick DW, Campbell JK. Cluster headache: diagnosis, management and treatment. In: Silberstein SD, Lipton RB, Dalessio DJ, eds. *Wolff's Headache And Other Head Pain*. 7th ed. New York, NY: Oxford University Press; 2001:283-309.

SURGICAL PROCEDURES FOR CLUSTER HEADACHES

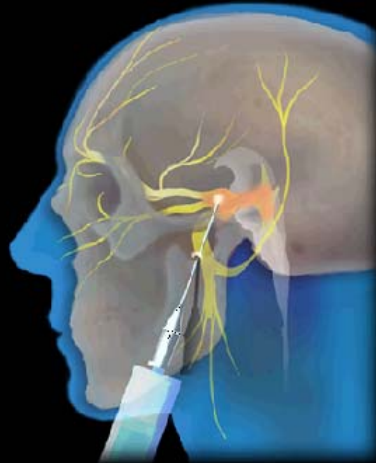
Sensory trigeminal pathway procedures

- Radiofrequency or glycerol rhizotomy
- Gamma knife radiosurgery
- Trigeminal root section

Autonomic (parasympathetic) pathway procedures

Hypothalamic stimulation

Occipital nerve stimulation



Mathew NT, Hurt W. *Headache*. 1988; Onofrio BM, Campbell JK. *Mayo Clin Proc*. 1986; Taha JM, Tew JM. *Headache*. 1995.

Of the surgical procedures attempted for the treatment of medically resistant cluster headache, those directed toward the sensory trigeminal nerve, rather than the autonomic pathways, have been the most effective. Trigeminal ganglion thermocoagulation with radiofrequency energy has been the most frequently performed destructive procedure for cluster headache. Approximately 75% of patients undergoing radiofrequency rhizotomy show good to excellent results (1,2). Only 20% of patients experience recurrence in the long term, and some even remain pain-free 20 years after the procedure (3).

1. Onofrio BM, Campbell JK. Surgical treatment of chronic cluster headache. *Mayo Clin Proc*. 1986;61:537-544.
2. Mathew NT, Hurt W. Percutaneous radiofrequency trigeminal gangliorhizolysis in intractable cluster headache. *Headache*. 1988;28:328-331.
3. Taha JM, Tew JM. Long-term results of radiofrequency rhizotomy in the treatment of cluster headache. *Headache*. 1995;35:193-196.

NEW TREATMENT HORIZON

Deep Brain and Occipital Nerve Stimulation

- 12 patients with refractory chronic cluster headache

- Stimulating electrode implanted into periventricular hypothalamus ipsilateral to pain

- Occipital nerve stimulation may be promising less invasive modality

Leone M et al. *Cephalalgia* 2003
Vandenheede M, et al *Cephalalgia* 2003



PET imaging has demonstrated activation of the homolateral posterior inferior hypothalamic gray matter during cluster headache attacks, a finding that appears to be specific to the condition. Leone and colleagues reported experimental deep brain stimulation of this area to prevent activation and relieve intractable cluster headache.

Case Review: A 39-year-old patient reported a 5-year history of medication refractory, excruciating cluster headaches that lasted 30 minutes to 4 hours, which occurred 2 to 5 times daily. Ninety percent of these were on the right side with the remainder on the left. No bilateral attacks were experienced. The patient had already undergone two percutaneous thermal rhizotomy procedures that resolved right-sided headaches; but left-sided headaches developed that mirrored the previous condition. Left-sided trigeminal surgery was contraindicated because of the high risk of blindness.

A Medtronic Activa Therapy deep brain stimulation system (commonly used to treat Parkinson's disease and essential tremor) was stereotactically implanted 6 mm posterior to the midpoint between the anterior and posterior commissures, 2 mm left of the midline, and 8 mm below the commissural plane. Following successful intraoperative stimulation with no adverse effects, the permanent neurostimulator was implanted subclavically and connected to the implanted electrodes via a subcutaneous tunnel. Therapeutic stimulation was continuous and unipolar at 180 Hz, 3 V, and a pulse width of 60 μ sec. Attacks disappeared 48 hours after stimulation was provided. The patient has remained pain-free for 13 months except for 2 occasions when stimulation was accidentally discontinued. In the absence of stimulation, headaches recurred. Reactivation of neurostimulation resolved the headaches.

Leone M, Franzini A, Bussone G. Stereotactic stimulation of posterior hypothalamic gray matter in a patient with intractable cluster headache. [Letter] *N Engl J Med.* 2001; 345(19):1428-1429.

Vandenheede M, Di Clemente L, Fumal A, et al. Deep brain stimulation in chronic cluster headache: a study of efficacy and mode of action in the first Belgian patients. *Cephalalgia* 2003;23(7):733.