APPLIED EVIDENCE
New research findings that are changing clinical practice

Practical strategy for detecting and relieving cluster headaches

Diagnosis, too often delayed, is not difficult given the typical pattern, and treatment options work for most patients

Practice recommendations
■ Learn to recognize the distinctive pattern of cluster headaches that in most cases, even if some symptoms suggest migraine, will readily reveal this disorder (C).
■ 100% oxygen by face mask and injected sumatriptan (Imitrex) are effective choices to terminate an acute attack (B).
■ Verapamil (Calan) or corticosteroids abort cluster cycles and prevent further attacks (B).

You interview a “migraine” sufferer who hopes to find the relief that has so far eluded him. During the history taking, he reports experiencing the premonitory aura typical of migraine as well as photophobia and occasionally nausea. One description, though, raises a question about the cause of his headaches: he says the intense pain recurs at roughly the same time of day and lasts for about 45 minutes; he is unable to concentrate on anything but the pain and he paces ceaselessly until it abates. The odds now favor a diagnosis of cluster headache.

Given that symptoms of migraine and cluster headaches overlap, and that migraine is more prevalent than cluster headache, recognizing the latter requires sensitivity to its key attributes described in this article.

Careful selection of therapeutic agents will hasten resolution of acute pain and prevent recurrences. Some drugs may be combined for quicker onset of action.

■ Telltale characteristics of cluster headaches
As shown in the opening example, cluster headache is diagnosed primarily by history.

Recognize the pattern. Its most striking feature is the unmistakable pattern of repeated bouts of pain that “cluster” at the same time of the day or night.

Each attack is extremely intense and brief, typically lasting 15 to 180 minutes.

For patients with the episodic variety of cluster headaches, the pattern of repeated headaches may last days to weeks, then resolve spontaneously. The relatively few patients with the chronic form of the disorder experience an unending cycle of daily or near daily headaches.

Attacks may occur during the day or night, and often wake the patient from sleep.†

Pain is always unilateral. Location of the pain varies among patients but is usually within the distribution of the trigeminal

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Cluster headaches have a striking pattern of intense and brief attacks that recur at the same time of the day or night. Almost all patients (92%) have retro-orbital pain, and most (70%) also have pain in the temporal region. Pain is present in the upper teeth, jaw, forehead, or cheek half of the time. Less common sites of pain are the ears, lower jaw, neck and shoulder.

Look for associated findings. Pain is accompanied by signs and symptoms of ipsilateral autonomic dysfunction. Lacrimation on the affected side is the most common associated feature. Rhinorrhea or a blocked nasal passage, red eye, and swelling or pallor of the forehead or cheek are often found bilaterally but are clinically dominant on the symptomatic side.

Restlessness occurs during an attack and the patient often prefers to pace about, in striking contrast to the migraine sufferer, who avoids activity so as not to exacerbate the pain. Half of cluster headache sufferers experience nausea, photophobia, or phonophobia during attacks. A smaller number (14%) report an aura similar to that of a migraine. Ninety percent of cluster headache patients who drink alcohol say it triggers headache while they are in the midst of a cluster cycle.

Delay in diagnosis common. The 2004 revision of the International Classification of Headache Disorders, reflects our improved understanding of and ability to identify these disorders. The mean time to diagnosis of cluster headache has decreased from 22 years in the 1960s to 2.6 years in the 1990s, reflecting much better recognition of the syndrome. Nevertheless most patients consult three primary care physicians before a diagnosis is made. The time between the first episode and diagnosis ranged from 1 week to 48 years (median 3 years) in one recent study.

Overlap of migraine and cluster symptoms may lead to misdiagnosis. Factors contributing to diagnostic delay include photophobia or phonophobia, nausea, an episodic attack pattern and a younger age at onset ($P<.01$). Correct diagnosis is further complicated in that 26% of cluster headache sufferers also report a history of

The hypothalamus is believed to be the source of cluster headaches. Its posterior cells regulate autonomic function and the anterior nuclei serve as the major circadian pacemaker. The elevation of plasma trace amine levels, including tyramine, octopamine, and synephrine in both migraine and cluster headache supports the hypothesis that disorders of biogenic amine metabolism may be a characteristic biochemical trait in primary headache sufferers. The trigeminal innervation of the dura and its vessels has a prominent role in the mechanism of cluster headache. Positron emission tomography, single photon emission computerized tomography, and functional MRI have augmented the growing clinical evidence that these headaches originate from the brain, rather than from a purely vascular cause.
migraine headaches. The key differentiating factor between the two headache types is the predictable pattern of repeated, intense, brief head pain.

**Rare underlying causes.** A very few patients with headaches have brain tumors. Headache is present in 50% to 60% of newly diagnosed brain tumors, but is usually accompanied by other signs or symptoms. It is the only presenting symptom in approximately 8% of cases. Most headaches due to tumors are clinically similar to tension headache (77%), and some mimic migraine (9%). Rapidly growing tumors are more likely to be associated with constant unremitting headache. Rarely brain tumors may produce pain syndromes similar to cluster headache. Other causes of secondary cluster headache include infections, vascular abnormalities, and head trauma.

A new subclassification of primary headache, trigeminal autonomic cephalgia, incorporates cluster headache with several other rarer types of headache that can be difficult to distinguish from primary cluster headache. Differentiation is important because the non-cluster types respond dramatically to indomethacin, whereas cluster headaches do not (TABLE 1).

### The 2 goals of treatment
Terminating acute headache is the first goal; shortening or aborting the cluster cycle is the second.

Research in the treatment of cluster headaches has been hampered by the relative infrequency of the condition, the short duration of each episode, and a robust placebo response. Much of the available evidence for the efficacy of various treatments comes from small controlled studies and case series.

Episodic cluster headaches respond much more readily to therapy than do chronic cluster headaches. Remember that no single intervention will work for every patient, and that some options are highly effective only for a small percentage of patients.

Of the drugs discussed in this section, injectable sumatriptan for acute attacks and oral verapamil for prophylaxis of attacks have the best evidence of efficacy based on controlled clinical trials.

### TABLE 1: Comparison of headache features

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>CLUSTER</th>
<th>MIGRAINE</th>
<th>PAROXYSMAL HEMICRANIA</th>
<th>SUNCT*</th>
<th>HEMICRANIA CONTINUA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>15–180 min</td>
<td>4–72 hrs</td>
<td>2–30 min</td>
<td>5–240 sec</td>
<td>Continuous</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>Yes</td>
<td>Unusual</td>
<td>Yes</td>
<td>Yes</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Pain quality</td>
<td>Sharp, boring</td>
<td>Often pulsatile</td>
<td>Stabbing or pulsatile</td>
<td>Stabbing or pulsatile</td>
<td>Stabbing or pulsatile</td>
</tr>
<tr>
<td>Severity</td>
<td>Severe</td>
<td>Mod–severe</td>
<td>Severe</td>
<td>Severe</td>
<td>Mod–severe</td>
</tr>
<tr>
<td>Frequency</td>
<td>Predictable</td>
<td>Varies</td>
<td>&gt;5/day</td>
<td>3–200/day</td>
<td>Continuous</td>
</tr>
<tr>
<td>Laterality</td>
<td>Unilateral</td>
<td>Varies</td>
<td>Unilateral</td>
<td>Unilateral</td>
<td>Unilateral</td>
</tr>
<tr>
<td>Response to Indomethacin</td>
<td>Not usually</td>
<td>Not usually</td>
<td>Always</td>
<td>Always</td>
<td>Always</td>
</tr>
</tbody>
</table>

*SUNCT, short-lasting neuralgiform headache attacks with conjunctival injection and tearing.
*Source: Lipton et al, Neurology 2004.*
Terminating acute headaches is the first goal; injectable sumatriptan has shown the best evidence of efficacy.

### TABLE 2

<table>
<thead>
<tr>
<th>DRUG</th>
<th>RESPONSE</th>
<th># OF PTS</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan 6 mg subcut. vs placebo&lt;sup&gt;13&lt;/sup&gt;</td>
<td>74% response @ 15 min 26% placebo response</td>
<td>39</td>
<td>2.1</td>
</tr>
<tr>
<td>Sumatriptan nasal vs placebo&lt;sup&gt;13&lt;/sup&gt;</td>
<td>57% response @ 30 min 26% placebo response</td>
<td>118</td>
<td>3.2</td>
</tr>
<tr>
<td>Sumatriptan subcut. vs sumatriptan nasal&lt;sup&gt;14&lt;/sup&gt;</td>
<td>94% response to injection @ 15 min 13% response to nasal</td>
<td>49</td>
<td>1.2</td>
</tr>
<tr>
<td>Zolmitriptan 10 mg orally vs placebo&lt;sup&gt;14&lt;/sup&gt;</td>
<td>47% response @ 30 min 29% placebo response</td>
<td>124</td>
<td>5.6</td>
</tr>
<tr>
<td>Octreotide 100 µg subcut. vs placebo&lt;sup&gt;14&lt;/sup&gt;</td>
<td>52% response @ 30 min 36% placebo response</td>
<td>46</td>
<td>6.3</td>
</tr>
<tr>
<td>Verapamil 120 mg orally 3x daily vs placebo&lt;sup&gt;17&lt;/sup&gt;</td>
<td>80% response in 2nd week</td>
<td>15 each arm</td>
<td>1.2</td>
</tr>
<tr>
<td>Oxygen 100%&lt;sup&gt;13&lt;/sup&gt;</td>
<td>75% with significant pain relief within 15 min</td>
<td>52</td>
<td>—</td>
</tr>
<tr>
<td>Dihydroergotamine IV&lt;sup&gt;13&lt;/sup&gt;</td>
<td>73% relief refractory episodic cluster 63% relief refractory chronic cluster</td>
<td>60</td>
<td>37</td>
</tr>
<tr>
<td>Lithium 900 mg daily vs Verapamil 360 mg daily&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Lithium: 37% improve in 1st week Verapamil: 58% improve in 1st week</td>
<td>24</td>
<td>4.8</td>
</tr>
<tr>
<td>Eletriptan 40 mg twice daily x 6 days&lt;sup&gt;21&lt;/sup&gt;</td>
<td>40% fewer attacks</td>
<td>16</td>
<td>—</td>
</tr>
</tbody>
</table>

#### Terminating acute headaches

**100% oxygen.** One hundred percent oxygen, delivered by face mask at high flow rates, has been shown to reduce the severity of cluster headaches or terminate acute attacks (TABLE 2). Absence of side effects is the real advantage of this therapy; the major drawback is the lack of portability of an adequate oxygen supply (strength of recommendation [SOR]: B).<sup>23</sup>

**Triptans.** Subcutaneous sumatriptan has been shown to provide relief for 88% of users (number needed to treat [NNT]=2.1), and its effectiveness seems not to wane with repeated use. The preferred dose is 6 mg; higher doses have been studied and are no more effective (SOR: A).<sup>23</sup> Intranasal sumatriptan is also effective, although less so than the parenteral form (NNT=3.2).<sup>15</sup> Oral zolmitriptan (Zomig) has shown benefit in approximately 60% of cases with both the 5- and 10-mg doses in episodic cluster headaches (NNT=5.6), but is no more effective than placebo in chronic cluster patients.<sup>15</sup>

**Side effects.** Most patients report side effects with triptans,<sup>24</sup> the most common being “atypical sensations” such as tingling, heat, pressure, tightness, numbness, or flushing. Dizziness and sedation can also occur, and, with injectable sumatriptan, reactions at the injection site are common. Before prescribing injectable sumatriptan, supervise administration of the first dose.

**Caveats.** Triptans are contraindicated for patients with vascular disease (coronary artery disease, stroke, peripheral vascular disease), renal, or liver dysfunction. Triptans should be used with caution by persons with multiple risk factors for coronary disease. They cannot be used in combination with other triptans or within
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24 hours of the use of dihydroergotamine (DHE 45).25

**Dihydroergotamine.** DHE can be used to terminate acute attacks using intravenous, subcutaneous, or intramuscular routes of administration (SOR: B). The usual dose is 1 mg, and many clinicians administer 10 mg of metoclopramide (Reglan) simultaneously to counter nausea (SOR: C). Complete familiarity with the proper use and potential adverse effects of injectable DHE is critical before using it in the outpatient setting.

Like triptans, DHE is contraindicated for those with vascular disease or severe liver or kidney impairment. Side effects include numbness or tingling in the extremities, muscle cramps, palpitations, and pain or tightness in the chest. Pleural and retroperitoneal fibrosis has occurred following prolonged daily use of ergots, and the use of DHE in patients with unrecognized coronary artery disease has caused death.

DHE levels are elevated by concurrent use of cytochrome P450 3A4 inhibitors such as macrolide antibiotics, protease inhibitors, ketoconazole, and itraconazole.26

**Other abortive agents.** There is little evidence for the use of other abortive agents. This poses a significant problem for the patient with cluster headaches who cannot take vasoconstrictors. A study of 5 patients showed olanzapine (Zyprexa), 2.5 to 10 mg, is a potentially effective abortive agent,27 and a larger study showed that octreotide (Sandostatin), 100 µg subcutaneously, relieved 52% of cluster headaches (NNT=6.3). Intranasal lidocaine has been shown to provide relief for 55% of migraine headaches, and some recommend its use in cluster headache.

**Prevention and interruption of the cluster cycle**

More important than aborting the acute headache is ending the cluster episode.

**Verapamil.** Ample evidence supports the effectiveness of verapamil (Calan) for this purpose (NNT=1.2).17 Larger doses than are typical for hypertensive therapy may be required.

**Cluster headache demographies**

**Cluster headache** is the most severe primary headache, is rare compared with other types of headache. Thus, despite severe head pain, the diagnosis may be overlooked.6 Studies in which the diagnosis was clinically confirmed reveal a prevalence ranging from 56 to 381 cases per 100,000 people.29 Cluster differs from migraine in that men are affected more commonly than women. Once believed to have a gender differential of 6:1, the ratio is now reported at 3:7:1.6

Age of onset also contrasts with migraine. Cluster headaches typically begin at around 30 years of age with a range of 20 to 50 years, but rarely as old as 80 years. Women are more likely than men to have onset in later years.

Most patients are smokers or former smokers (74%), but cessation of smoking does not appear to modify the pattern of headaches.

Inheritance plays a greater role than previously realized, suggesting a genetic cause. First-degree relatives have a 5- to 18-fold higher risk for cluster headache than the general population. Second-degree relatives have a 1- to 3-fold higher risk. The mode of inheritance is likely autosomal dominant with low penetrance in some families, and multifactorial inheritance or autosomal recessive in other families.29

A regimen of 40 mg in the morning, 80 mg at noon, and 80 mg at bedtime, allowing patients to titrate doses up by 40 mg on alternate days, relieved 94% of episodic cluster headaches and 55% of chronic cases (SOR: B).29 Most patients need 200 to 480 mg/d to achieve success, but some require up to 960 mg/d.30

If a patient is asymptomatic but has a history consistent with cluster headaches, and if your examination reveals no other cause of headache, a trial of verapamil is warranted to abort the cluster cycle or prevent additional cycles.

**Other agents.** Corticosteroids may act faster than verapamil, and the two can be used in combination (SOR: C). A typical regimen of prednisone starts with 40 mg/d and tapers over 3 weeks.24

Lithium (Lithobid, Eskalith) is effective, but acts slowly and causes more side effects than other agents.20

Other agents that have shown efficacy in small studies are gabapentin,
Applied Evidence

when to refer

Treatment for most cluster headache sufferers is adequately handled in the primary care setting. When medical therapy fails, consider referral to a headache specialist, particularly for those with chronic cluster headaches. In some cases, sympathetic nerve blockade might be a worthwhile consideration. Unfortunately, a small subset of patients will not find relief regardless of the regimen employed.

References


28. Freitag FG. Cluster headache. Primary Care; Clinics in Office Practice 2004; 31(no 2), June.


