The International Headache Society classifies headache disorders into primary and secondary disorders [1]. Table 146-1 lists the primary headache disorders.

**Migraine**

In an epidemiological study of migraine [2] using a self-administered questionnaire filled out by 23,611 individuals from 9,507 American households, 17.6% of women and 5.7% of men between ages 12 and 80 years had headaches that met a definition of migraine that was based on a modification of the International Headache Society’s criteria [1]. Projections from this study to the country as a whole indicate that 18 million women and 5.6 million men over age 12 suffer from severe migraine headaches. Diagnostic criteria for migraine with and without an aura are given in Table 146-2.

Among these individuals, a projected 8.7 million women and 2.6 million men have moderate to severe disability from headache [2]. Fifty-five percent of men and seventy-two percent of women never consult a doctor for a headache problem [3]. Among those who seek medical attention, 44.5% of men and 46.3% of women consult family practitioners. With increasing awareness of headache as a biological problem, it is expected that a larger number of migraine patients will seek help for this condition.

Migraine can occur with or without an aura (warning symptoms). The most common aura is visual in nature, although neurological auras such as hemisensory disturbances, hemiparesis, dysphasia, and changes in memory and state of consciousness occur occasionally. Migraine without aura is far more common than migraine with aura; approximately 30% of migraine attacks are associated with aura. The same person can have migraine with aura and migraine without aura at different times. Migraine is predominantly a disease of females. Identification of trigger factors for attacks of migraine helps in making the diagnosis. The trigger factors are listed in Table 146-3. The severity and frequency of attacks vary over time. Cyclical exacerbations of migrainous episodes are possible during one’s lifetime.

A migraine attack is typically episodic, occurring once or twice a month, and is manifested in many phases. The prodrome phase consisting of symptoms of excitation or inhibition of the central nervous system, including elation, excitability, irritability, increased appetite, craving for sweets, or excessive yawning, depression, sleepiness, and tiredness, occurs in 30% of patients. These symptoms may precede the attack by 12–24 h. The prodrome phase may be followed by the aura phase, which consists of specific visual or neurological symptoms. The headache phase is the most prominent part of the migraine attack. The headache is predominantly unilateral in at least 50% of patients, although it can be bilateral. It also may start on one side and switch to the other side. A pulsating quality of the head pain is seen in approximately 50% of these patients. Nonpulsating headache does not exclude migraine. The headache usually lasts from 4 to 72 h, and occasionally lasts longer. It is associated with gastrointestinal symptoms such as nausea and/or vomiting and diarrhea in 90% of patients. Heightened sensory perception, including phonophobia, photophobia, and increased sensitivity to smell, occurs during the
attacks. Patients usually want to be left alone, and the attacks can be very disabling.

The headache of migraine is of moderate or severe intensity (inhibits or prohibits daily activities) as opposed to episodic tension-type headache, in which the intensity is mild to moderate (may inhibit but does not prohibit daily activities). The headache of migraine is aggravated by any activity that increases stroke volume or intracranial pressure, such as climbing stairs, jogging, running, bending down, and coughing. During the headache, at least one of the following characteristics occurs: (1) nausea and/or vomiting and (2) photophobia and phonophobia. These symptoms are necessary for a diagnosis of migraine. Physical and neurological examinations should rule out any other structural or metabolic condition that can cause headache.

### Menstrual Migraine

Migraine without aura can occur almost exclusively at a particular time in the menstrual cycle. True menstrual migraine occurs between 2 days before menses and the last day of menses. Migraine also can occur as a part of the late luteal phase disphoric disorder (premenstrual tension). Migraine attacks are not uncommon during ovulation. Menstrual migraine is less responsive to prophylactic drug therapy than other types of migraine.

Status migrainosus refers to a prolonged migraine attack that usually lasts for more than 72 h and is associated with nausea, vomiting, and dehydration. These patients usually are extremely sick and dehydrated and may have to be
hospitalized. By the time they come to the emergency room, they may have already tried large quantities of analgesic medications and/or ergotamine with no benefit.

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**Cluster Headache**

Cluster headache is predominantly a disease of males. These headaches are almost always
unilateral and short-lived, usually lasting about 45 min to an hour. Multiple episodes occur on a daily basis for periods of 2 or 3 months, with remissions lasting for a number of months to years, with headaches returning in a cluster fashion again for 2 or 3 months. Cluster pattern and remissions are characteristics of the disease, even though in approximately 10% of patients there are no remissions (chronic cluster headache). Associated with the pain are autonomic features such as watering from the eyes, redness of the eyes and congestion of the conjunctiva, and ipsilateral stopping up of the nostrils during the attack. The International Headache Society diagnostic criteria are given in Table 146-4.

### Episodic Tension-Type Headache

The most common type of headache is the episodic tension-type headache, for which patients rarely consult a doctor. This type of headache usually is pressing or tightening in quality, bilateral, mild to moderate in severity, and occasionally associated with very mild nausea, photophobia, or sonophobia. There is no vomiting, and the patients are able to carry on with their activities. The headache is not aggravated by physical activity.

### Chronic Daily Headache

Even though the term chronic daily headache is not included in the International Headache Society classification, from a practical point of view it is important. Chronic tension-type headaches are one of the types of chronic daily headache. The clinical features of chronic tension-type headache are essentially the same as those of the episodic tension-type except that the headache occurs more than 180 days a year. The comorbid factors often seen in chronic tension-type headache include anxiety, depression, excessive intake of pain medications, abnormal personality profiles, inadequate personality, and repressed anger.
Both episodic and chronic tension-type headaches can be associated with pericranial muscle tenderness and a low pain threshold. Digital palpation of the pericranial muscles, including the neck muscles, reveals increased stiffness and tenderness. The migraine chronic tension-type headache complex (mixed headache) manifests as daily or nearly daily headaches that show features of migraine and chronic tension-type headache in a mixed form. Many patients have episodes of severe headache with migrainous features, with interictal tension-type headache occurring very frequently. Many of these patients have a history of episodic migraine that gradually evolves into daily headache (transformed migraine) [4]. It sometimes becomes difficult to identify the termination of one type of headache and the beginning of the other type. There are two distinguishable forms in this variety of headache: those associated with analgesic and ergotamine overuse and those not associated with drug overuse. It is well known to specialists in headache that daily or nearly daily use of analgesics and ergotamine in patients with migraine can lead to a chronic daily intractable headache condition that is referred to as an analgesic/ergotamine rebound headache. It is important to look for this disorder in any patient who presents with chronic headaches. Analgesic/ergotamine rebound headache is refractory to regular treatments. The patients show many associated features, such as early morning awakening with severe headaches; sleep disturbances; tolerance to pain medications over a period of time, requiring larger quantity of medications; and manifestation of withdrawal symptoms when the medications are stopped. In addition, prophylactic antimigraine medications become ineffective as long as the patients are on daily pain medications or ergotamine.

Posttraumatic Headache

Headache can follow relatively minor head and neck trauma, and previously dormant migraine can be aggravated by trauma. Patients with posttraumatic headache usually manifest a mixed form of migraine and tension-type headache with considerable detectable neck muscle spasm and pericranial tenderness.

Most headache specialists believe that the various clinical headache types are different manifestations of the same primary disorder, which presents as migraine with aura at one end of the spectrum, chronic tension-type headache at the other, and a combination of migraine without aura and tension-type headache in the middle [5]. Many patients who present with chronic daily headaches have what is described as “transformed migraine” that is, they report a history of clear-cut episodic migraine with increasing frequency of headache until they eventually end up with daily or nearly daily headaches, many of which retain features of migraine [4].

Biological Basis of Migraine Pharmacotherapy

The two basic theories that have been postulated to explain the mechanisms of migraine are vascular and neurogenic, with considerable debate about whether migraine is primarily a cephalic vascular disorder or a disorder of the central nervous system (CNS).

The vascular theory of migraine proposes that intracerebral vasoconstriction accounts for the aura or migraine, while intracranial and extracranial vasodilation accounts for the head pain. A lack of correlation between the observed changes in cerebral blood flow [6,7] and the occurrence of head pain in patients who have migraine with aura has led to the conclusion that vascular reactions may be associated with symptoms of headache but do not necessarily trigger an attack. Instead, recent clinical and experimental evidence strongly points to migraine as a disorder initiated in the brain and accompanied by secondary changes in the perivascular...
nerve endings of the cephalic circulation that result in neurogenic inflammation.

**The Trigeminal Vascular System**

A series of studies by Moskowitz and colleagues [8] established the trigeminal vascular system as the common final pathway for head pain. The perivascular C fibers of the trigeminal nerve in the cephalic circulation are the site of neurogenic inflammation that can be produced by antidromic stimulation of the trigeminal nerve [8].

Neurogenic inflammation is triggered by elaboration of vasoactive polypeptides such as substance P, neurokinin A, and calcitonin gene-related polypeptide (CGRP). The neurogenic inflammation consists of platelet aggregation, protein extravasation, and vasodilatation. These changes initiate nociception through perivascular C fibers.

Stimulation of the cranial vascular systems, such as the superior sagittal sinus, results in an increase in CGRP in the jugular blood in experimental animals [9]. Goadsby and Edvinsson [10] showed that during a migraine attack the level of CGRP in the external jugular vein increases.

These observations undoubtedly prove that the trigeminal vascular system is involved in acute migraine attacks. The ultimate initiating trigger of a migraine attack may reside in the brain, which in turn activates the trigeminal vascular system.

**Central Neuronal Hyperexcitability in Migraine**


Glutamate, an excitatory amino acid, has been implicated in the pathogenesis of migraine, since it may play a role in spreading depression experimentally [14]. Abnormalities in platelet glutamate levels have been reported in patients with migraine [15].

**Brain Stem Migraine Generator**

Brainstem structures that are implicated in the pathogenesis of migraine and have relevance to pharmacotherapy include the dorsal raphe nuclei and periaqueductal gray matter. Raskin and coworkers [16] indicated that perturbation or dysfunction of the dorsal raphe nuclei, resulting in an increased firing rate of the raphe cells, may be one of the fundamental abnormalities in migraine. Sleep, which reduces the firing rate of dorsal raphe cells, is known to relieve migraine headache. Recently, using positron emission tomography (PET) scanning, increased perfusion of the upper brain stem area close to the dorsal raphe and periaqueductal gray matter was demonstrated in patients during migraine attacks [17]. These observations suggest the upper brain stem as a generator of migraine.

The dorsal raphe nuclei are one of the major binding sites of dihydroergotamine mesylate (DHE), a very effective therapy for acute migraine [18]. The dorsal raphe nuclei contain large numbers of serotonergic cells, suggesting that DHE and related medications may act through the serotonergic system.

**Serotonin and Migraine**

Serotonin [5-hydroxytryptamine (5-HT)] has long been implicated in the pathogenesis of migraine. Initial observations included the precipitation of
migraine by reserpine, a serotonin-depleting agent, [19] and relief of migraine by the injection of serotonin even though severe side effects limit its clinical use [20]. Serotonin metabolites are increased in urine during an attack, [21] and plasma serotonin levels fall just before a migraine attack [22].

Medications that act on the serotonin system have long been used in the treatment of migraine. Table 146-5 shows the chronological order in which serotonin-related medications have been used in migraine. In recent years, there has been a great deal of interest in serotonin pharmacology. At least three major classes of serotonergic receptors have been identified: 5-HT₁, 5-HT₂, and 5-HT₃. 5-HT₁D and 5-HT₁A are probably the most relevant serotonin receptors in relation to the pharmacology of an acute migraine attack.

In general, it appears that medications with an affinity for 5-HT₁ receptors are effective in the treatment of acute migraine attacks and that medications that have an antagonist affinity for 5-HT₂ are useful in migraine prophylaxis [23]. The relative affinities for 5-HT₁ are shown in Table 146-6.

It has been shown that pretreatment with sumatriptan and DHE, both of which are 5-HT₁ agonists, can block the neurogenic inflammation that can be induced by antidromic stimulation of the trigeminal nerve [24,25]. In addition, these medications reduce or prevent the increase in CGRP in the jugular blood induced by craniovascular stimulation [9] and during migraine attacks [26].

Researchers do not fully agree on the mechanism of action of 5-HT₁ agonists in migraine. On the basis of their experiments, Moskowitz and colleagues strongly believe that 5-HT₁D receptors are located on the C fibers of the perivascular nerve endings. The agonistic action of sumatriptan and ergot alkaloids on 5-HT₁D receptors blocks the neurogenic inflammation at the level of the nerve ending. They also have shown that 5-HT₁D receptor agonists, in addition to blocking neurogenic inflammation, may reduce pain transmission through the trigeminal nerve; this conclusion was based on experiments using c-fos markers [27]. However, Humphrey and coworkers [28] believe that the effect of sumatriptan is primarily due to craniovascular vasoconstriction and closure of the arteriovenous anastomosis, which is postulated to be one of the mechanisms of migraine head pain [29]. It should be noted that sumatriptan has very little peripheral vasoconstrictive effect and is predominantly a selective craniovascular agent.

<table>
<thead>
<tr>
<th>Table 146-5</th>
<th>Chronological Order in which 5-HT medications were introduced into migraine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin-related drug</td>
<td>Year</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>1928</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>1945</td>
</tr>
<tr>
<td>Methysergide</td>
<td>1959</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>1964</td>
</tr>
<tr>
<td>Pizotifen</td>
<td>1968</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>1973</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>1991</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 146-6</th>
<th>Antimigraine drug relative potencies at 5-HT₁D receptor subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimigraine drug</td>
<td>Relative affinity for 5-HT₁D receptor</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td>Acute</td>
<td></td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>17</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>19</td>
</tr>
<tr>
<td>Prophylactic</td>
<td></td>
</tr>
<tr>
<td>Methysergide</td>
<td>120</td>
</tr>
<tr>
<td>Pizotifen, alprenolol, amitriptyline, cypheptadine, nifedipine, pindolol, propranolol, verapamil, timolol, atenolol, or diltiazem</td>
<td>&gt;1,000</td>
</tr>
</tbody>
</table>

Adapted from Peroutka SJ: Development of 5-hydroxytriptamine receptor pharmacology in migraine. Neurol Clin 8:831, 1990. With permission
Treatment of Acute Migraine Attacks

Factors that determine the choice of medications for acute migraine are time to reach maximum headache (time to peak), severity, and associated symptoms such as nausea and vomiting. The frequency of attacks combined with their severity determine prophylactic pharmacotherapy.

The main principle of the treatment of acute migraine is the use of medications early in an attack. This is especially relevant for oral medications, which should be administered long before nausea and vomiting set in. For practical purposes, it may be worthwhile to divide acute migraine attacks into different treatment categories, depending on the severity of the attack (Table 146-7).

Mild to Moderate Attacks

For mild to moderate attacks, simple analgesics such as aspirin and acetaminophen may be all that is necessary. There is an associated gastroparesis in migraine that results in poor absorption of aspirin from the large intestine [30]. Phenothiazines such as promethazine, which are commonly used as antiemetics, have a tendency to reduce gastric motility further, resulting in delayed absorption of aspirin. Therefore, metoclopramide, which increases gastric motility and enhances the absorption of aspirin, is the antiemetic of choice in patients with acute migraine attacks.

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as rapidly absorbed naproxcen sodium are effective for the abortive treatment of mild to moderate cases of migraine. Isometheptene mucate (available in combination with dichloralphenazone and acetaminophen) is also a very useful agent for abortive migraine treatment. Isometheptene is a sympathomimetic vasoconstrictor, and its exact mechanism of action is unknown. Since it is well tolerated by most people, it is the drug of choice for mild to moderate attacks.

Moderate to Severe Attacks

Until recently, ergotamine tartrate was the drug of choice for moderate to severe episodes of migraine. Ergotamine, alone or in combination with caffeine, is available in oral and rectal forms. If the patient is not nauseated, oral ergotamine is useful and can be combined with NSAIDs such as naproxcen sodium and meclofenamate. Meclofenamate alone has been shown to have an antimigraine effect comparable to that of ergotamine, [31] and we find this combination useful. Injectable ketorolac has been very effective in some patients with moderate to severe migraine and has been recommended as a practical alternative to narcotic injections [32].

If the patient is nauseated, metoclopramide is often the antiemetic of choice. Since metoclopramide is a dopamine agonist, it may cause extrapyramidal reactions in the form of akathisia and restlessness.

<table>
<thead>
<tr>
<th>Time to peak, h</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>Sumatriptan 6 mg subcutaneous</td>
</tr>
<tr>
<td></td>
<td>DHE 1 mg intramuscular</td>
</tr>
<tr>
<td></td>
<td>Nasal butorphanol 1–2 mg</td>
</tr>
<tr>
<td>1–3</td>
<td>Sumatriptan tablets 50 mg; repeat 50 mg at 2 h</td>
</tr>
<tr>
<td></td>
<td>Ergotamine suppository 2 mg (Wigraine, Cafergot)</td>
</tr>
<tr>
<td></td>
<td>DHE nasal spray 2 mg</td>
</tr>
<tr>
<td>&gt;3</td>
<td>Isometheptene compounds (Midrin); 2 capsules, repeat 1 in 1/2 h</td>
</tr>
<tr>
<td></td>
<td>Ergotamine tablets</td>
</tr>
<tr>
<td></td>
<td>2 mg or ergotamine 1 mg with naproxcen 550 mg or meclofenamate 200 mg</td>
</tr>
<tr>
<td></td>
<td>Sumatriptan 50-mg tablets; repeat 1 in 2 h</td>
</tr>
</tbody>
</table>
Drugs Used to Treat Migraine

**Sumatriptan**

Sumatriptan is a 5-HT1D agonist that blocks neurogenic inflammation at the trigeminal vascular system and causes vasoconstriction. It is available in tablet and subcutaneous forms. Sumatriptan has become the drug of choice in the treatment of moderate to severe cases of migraine.

Our knowledge of sumatriptan use in acute migraine is based on major clinical trials [33–35]. With subcutaneous injection, the onset of relief occurs in 10–15 min; 50% of patients get relief in 30 min. More than 80% show relief in less than 2 h, and 60% become pain-free in 2 h. With tablets, the onset of relief occurs in 30 min. Sixty percent of these patients show improvement in 1 h, and 75% by 4 h. Nearly 50% are pain-free in 4 h.

Sumatriptan is effective any time during an attack, unlike ergotamine, which is most effective in the early part of an attack. Another important advantage of sumatriptan over ergotamine is that the accompanying symptoms of migraine, such as nausea and vomiting, are relieved by sumatriptan, obviating the need for a separate antiemetic agent. With sumatriptan, patients are able to return to their normal activities very rapidly.

Sumatriptan studies have shown that most of the adverse events are mild to moderate, occur early after the treatment, are of short duration, and resolve spontaneously. Electrocardiogram monitoring showed no more abnormalities with sumatriptan than with placebo. There are very few adverse reactions of any consequence, and as the data indicate, this is a relatively safe drug from a cardiovascular point of view. Typical adverse effects after subcutaneous injection of sumatriptan include tingling, a warm or hot feeling, heaviness of the upper part of the body, flushing, and a burning sensation of the head, but all these symptoms are mild and transient. Transient or pressure symptoms in the chest occur in 3–5% of these patients. There is no evidence that the pressure is of cardiac origin. In the postmarketing surveillance, the incidence of cardiac ischemia has been extremely low, occurring in 1 in 1 million migraine attacks treated with sumatriptan. Some of the cardiac symptoms reported were related to the use of sumatriptan in patients with preexisting cardiac disease or concomitant risk factors. Misinterpretation of clinical symptomatology (e.g., misdiagnosing a stroke in evolution for a migraine attack) and inappropriate dosing were also factors in previously reported complications of therapy with sumatriptan.

For subcutaneous injection, a 6-mg dose is the most effective and has the fewest side effects. For oral dosing, 25- or 50-mg tablets are used. Approximately 35% of patients have recurrence of the pain in 24 h, but data indicate that sumatriptan can be repeated in such cases with prompt relief of the recurrence. A practical way of using sumatriptan is as an injection followed by tablets. The injection gives immediate relief and the tablets continue to maintain adequate blood drug levels, and so pain does not recur within the first few hours.

**Dihydroergotamine**

For the treatment of severe to very severe migraine, parenteral medications may have to be used, since these patients are extremely sick with nausea and vomiting. Intravenous DHE is the drug of choice in such a situation. Dihydroergotamine can be combined with intravenous (IV) metoclopramide, prochlorperazine, or chlorpromazine.

Dihydroergotamine is a highly effective medication for acute migraine attacks but is underutilized. Its advantages include minimal arterial constriction and intravenous administration with far less nausea compared with ergotamine. One study comparing DHE with narcotics
showed that DHE is superior to meperidine and butorphanol tartrate in the acute treatment of migraine headache in the emergency room [36].

No physical dependence has been reported with DHE use. Peak plasma levels are attained in 15–45 min with subcutaneous injection, 30 min with intramuscular injection, 2–11 min with IV injection, and 30–60 min with intranasal administration. Self-injection by patients is possible.

Dihydroergotamine has an affinity for 5-HT\textsubscript{1A} and 5-HT\textsubscript{1D} receptors, and this probably accounts for its antimigraine effects. It also has an affinity for 5-HT\textsubscript{2} adrenergic receptors and dopaminergic receptors. Its affinity for dopaminergic receptors may account for the nausea that can occur as a side effect. The advantage of sumatriptan over DHE is that it has specific affinity for 5-HT\textsubscript{1} receptors only and has no effects on adrenergic or dopaminergic receptors; this accounts for the lack of nausea and vomiting as a side effect.

As was discussed earlier, DHE not only acts at the 5-HT\textsubscript{1} receptor sites and the trigeminal vascular system but also is bound to dorsal raphe nuclei and other brain stem serotoninergic nuclei. Therefore, the action may also be central [18].

Status migrainosus is defined in the International Headache Society’s classification as a prolonged migraine attack that lasts more than 72 h; is associated with nausea, vomiting, and other gastrointestinal (GI) symptoms; and is totally incapacitating. The patient usually presents to the physician after having taken fairly large quantities of pain medications and usually is dehydrated.

Hospitalization, IV fluids, and repeated injections of intravenous DHE for about 24–72 h may be necessary to relieve the headache. Various protocols are available for the use of repetitive injections of DHE [37,38]. In all of them, an initial test dose of 0.34 mg of DHE plus 5 mg of metoclopramide or prochlorperazine is given, followed by 0.5 mg of DHE with either of the two antiemetics every 6 h for 48–72 h.

Most patients are able to tolerate the medications used in these protocols. Intolerance to DHE can occur in a few patients because of severe nausea or vomiting in spite of antiemetics. Very rarely, its use may be limited by acute myalgia involving the lower extremities and numbness or paresthesia. Vasospastic reaction with angina has been reported but is rare.

Repetitive IV DHE is the mainstay in the treatment of status migrainosus at present. The concomitant use of narcotics is not recommended. In fact, analgesics and narcotics have no place in the treatment of status migrainosus and very little place in the treatment of recurrent episodes of acute migraine. Frequent use of analgesics and narcotics may result in the transformation of episodic migraine into chronic daily headache [39].

### Alternative Therapy for Acute Migraine

#### Intravenous Prochlorperazine

Patients who are not responsive to sumatriptan or IV or intramuscular DHE can be given IV prochlorperazine (Compazine) [40]. Compazine (5–10 mg) can be given intravenously in an emergency room setting. Dystonic reactions are possible in some patients who receive Compazine and can be counteracted by intramuscular injection of 1 mg of benztropine mesylate (Cogentin). Intravenous chlorpromazine (Thorazine) may also be worth trying in patients who do not respond satisfactorily to sumatriptan or DHE. From 12.5 to 25 mg (0.1 mg/kg) of chlorpromazine given in a piggy back IV is effective in many patients with acute migraine. Repeat dosing every 15 min up to a total of three doses may become necessary. Orthostatic hypotension is a distinct side effect, and patients have to be monitored for a while before they are allowed to get up and walk around or go home. They have
to be warned about the possibility of orthostatic hypotension.

**Narcotics and Sedatives in Acute Migraine**

Most migraine attacks can be managed without narcotics, using the medications mentioned above. The reasons why narcotics are not preferred in migraines are as follows:

1. Serotonin mechanisms are disturbed in migraine, and medications such as sumatriptan, ergotamine, and dihydroergotamine are 5-HT\textsubscript{1D} receptor agonists that reduce the neurogenic inflammation associated with migraine attacks in addition to their vasoconstrictive effect, whereas narcotics reduce pain without having any specific effects on the neurogenic inflammation or vasodilatation.

2. Narcotics and analgesics with sedatives may in fact produce rebound headache phenomena and perpetuate the chronicity of migraine.

3. With frequent use, habituation occurs.

For these reasons, narcotics are very rarely recommended for acute attacks of migraine. However, in a person who is totally nonresponsive to sumatriptan, ergotamine, DHE, and phenothiazines, one may use parenteral narcotics such as meperidine (Demerol) in a limited way; however, it should not be prescribed on a routine basis.

**Combination of Analgesics with Sedatives**

A number of preparations are available that contain butalbital with acetaminophen or aspirin and caffeine with or without codeine, including Fiorinal, Fiorinal #3, Fioricet, Fioricet with Codeine, Esgic, Esgic with Codeine, Esgic Plus, and Phrenilin. While these preparations are useful for a person with occasional migraine, they are certainly not recommended for patients with frequent episodes of migraine or tension-type headache. Not only do these medications have a potential for abuse, they also invariably produce rebound headache phenomena when used frequently. The excessive use of medications containing butalbital results in lethargy, sleepiness, lack of concentration, and an overall sedated feeling. One of the other major dangers in the use of butalbital-containing medications is that abrupt discontinuation may result in withdrawal phenomena such as increased headache, nausea, irritability, sleeplessness, and even seizures. Because of these problems with the combination medications containing butalbital, the author does not recommend them for routine use. If one has to use a narcotic oral pain medication, a combination of acetaminophen with 30 mg of codeine is probably the least controversial.

**Prophylaxis of Migraine Headaches**

**Prophylactic Pharmacotherapy**

The decision to start prophylactic pharmacotherapy, which has to be made on a daily basis, depends totally on the impact of migraine on the patient. This impact depends on the frequency, the severity, the disability headache produces, and the comorbid factors. In general, the following are the broad indications for prophylactic pharmacotherapy:

1. Two or more attacks per month that are disabling and result in inability to work or function
2. Severe, prolonged, disabling attacks even if they occur less than twice a month
3. Inability to cope with migraine episodes
4. Failure of abortive therapy
5. Serious side effects from abortive therapy
6. Failure of nonpharmacological approaches

Table 146-8 lists the currently used prophylactic agents for migraine.

Steps Before Prophylactic Pharmacotherapy

The following steps should precede prophylactic pharmacology:

1. Women of childbearing age should practice contraception, preferably barrier contraception
2. Vasodilators should be avoided as much as possible
3. Concomitant daily analgesics should be avoided

One should be alert to the fact that many of these patients have comorbid disorders, making the treatment difficult and the prognosis less than satisfactory. The comorbidity includes depression, anxiety, panic episodes, bipolar illness, and neuroticism. Analgesic and ergotamine rebound must be recognized, and those who are on daily analgesics or ergotamine should be detoxified from those medications before prophylactic pharmacotherapy is instituted. It is difficult to assess the success of prophylactic therapy because of variability in migraine frequency and severity and the tendency for spontaneous improvement for prolonged periods. In addition, it is well known that migraine can come in cycles in an unpredictable fashion, and this also makes the assessment of prophylactic therapy difficult. In some situations, tachyphylaxis to medications is observed.

It is important to give adequate time for prophylactic therapy to work. To judge the effectiveness of any medication used, one should treat

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-adrenergic blocking agents</strong></td>
<td></td>
</tr>
<tr>
<td>Propranolol (Inderal)</td>
<td>40–160 mg/day in divided doses</td>
</tr>
<tr>
<td>Propranolol long-acting (Inderal-LA)</td>
<td>60–160 mg once daily</td>
</tr>
<tr>
<td>Nadolol (Corgard)</td>
<td>40–160 mg once daily</td>
</tr>
<tr>
<td>Timolol (Blocadren)</td>
<td>Up to 20 mg twice daily</td>
</tr>
<tr>
<td>Metoprolol (Lopressor)</td>
<td>50–100 mg/day</td>
</tr>
<tr>
<td>Pindolol (Visken)</td>
<td>10–30 mg/day</td>
</tr>
<tr>
<td>Atenolol (Tenormin)</td>
<td>50–100 mg/day</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline (Elavil, Endep)</td>
<td>25–200 mg at bedtime</td>
</tr>
<tr>
<td>Doxepin (Sinequan, Adapin)</td>
<td>10–100 mg at bedtime</td>
</tr>
<tr>
<td>Nortriptyline (Aventyl, Pamelor)</td>
<td>10–50 mg at bedtime</td>
</tr>
<tr>
<td>Imipramine (Tofranil)</td>
<td>25–150 mg at bedtime</td>
</tr>
<tr>
<td>Desipramine (Pertofrane, Norpramin)</td>
<td>25–50 mg, at bedtime</td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>20 mg daily in the morning</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>50 mg at bedtime</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>20 mg daily in the morning</td>
</tr>
<tr>
<td><strong>Monoamine oxidase inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Phenelzine (Nardil)</td>
<td>15 mg three times daily</td>
</tr>
<tr>
<td>Isocarboxazid (Marplan)</td>
<td>10 mg four times daily</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Verapamil (Calan, Isoptin, Verelan)</td>
<td>80–360 mg/day</td>
</tr>
<tr>
<td>Flunarizine (Sibelium)α</td>
<td>10–30 mg/day</td>
</tr>
<tr>
<td>Diltiazem (Cardizem)</td>
<td>60–90 mg three times/day</td>
</tr>
<tr>
<td>Nicardipine (Cardene)</td>
<td>20 mg three times/day</td>
</tr>
<tr>
<td>Nimodipine (Nimotop)</td>
<td>30 mg three times/day</td>
</tr>
<tr>
<td><strong>Serotonin antagonists</strong></td>
<td></td>
</tr>
<tr>
<td>Methysergide (Sansert)</td>
<td>4–8 mg/day</td>
</tr>
<tr>
<td>Cyproheptadine (Periactin)</td>
<td>8–16 mg/day</td>
</tr>
<tr>
<td>Pizotifen (Sandomigran)α</td>
<td></td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
</tr>
<tr>
<td>Divalproex sodium (Depakote)</td>
<td>500–1,500 mg/day</td>
</tr>
<tr>
<td>Phenytoin (Dilantin)</td>
<td>100–300 mg/day</td>
</tr>
<tr>
<td><strong>Alpha-adrenergic agonist</strong></td>
<td></td>
</tr>
<tr>
<td>Clonidine (Catapres)</td>
<td>0.1–0.2 mg three times a day</td>
</tr>
</tbody>
</table>

αNot available in the United States
the patient at least for 2–3 months, particularly in the case of calcium channel blockers, which should be given for at least 3 months in adequate doses before they are judged to be ineffective. It is always good to start with small doses and gradually increase the dose in accordance with the tolerance of the patient. When patients are withdrawn from prophylactic therapy, this has to be done gradually.

Some Reasons for Prophylactic Treatment Failure

There are several possible reasons for treatment failure:

1. Wrong diagnosis
2. Not recognizing comorbidity
3. Not recognizing analgesic rebound phenomena
4. Inadequate dose
5. Inadequate treatment period
6. Unrealistic expectations on the part of the patient as well as the physician

Beta-adrenergic Blocking Agents

Beta-adrenergic blockers are considered the first line of treatment for migraine prophylaxis at present. Propranolol and timolol have been approved by the U.S. Food and Drug Administration (FDA), whereas the other agents, such as nadolol, have not been specifically approved. It is better to start with small doses and increase the dose gradually. If a person is not adequately responsive to one particular beta blocker, another can be tried.

There is no correlation between the efficacy of beta blockers and their ability to enter the CNS, their membrane stimulating properties, their 5-HT-blocking properties, or beta receptor selectivity. Beta blockers are best suited for patients with migraine who are under stress and are anxious. They are suitable for patients with migraine and hypertension.

Contraindications and Adverse Effects of Beta Blockers

Beta blockers are contraindicated in patients with active asthma, hypotension, congestive cardiac failure, and diabetes mellitus. Their main drawback is the side effects, which include weight gain, lethargy, extreme tiredness, and depression. Many patients have associated depression as a comorbid disorder, and beta blockers are not suitable for such patients.

Tricyclic Antidepressants

Tricyclic antidepressants, particularly amitriptyline, are widely used for migraine. They are not as efficacious as beta blockers. The side effects, which include weight gain and sleepiness, anticholinergic effects such as dry mouth, blurred vision, and dysuria, may become a problem. In selecting a tricyclic, one should take into consideration the anticholinergic effects. If a person has many symptoms pointing to anticholinergic activity, the patient may be switched from amitriptyline to nortriptyline, which has less of an anticholinergic effect. Those who want sedation at night may be tried on doxepin. Tricyclic antidepressants, particularly amitriptyline, have a central analgesic effect that has been shown to reduce the firing rate of the trigeminal nucleus caudalis. The antidepressant effect helps patients with migraine, and the hypnotic effect is helpful in many patients. Tricyclic antidepressants are particularly useful in patients with frequent attacks of migraine, migraine with medication overuse, migraine with sleep disorders, migraine with tension-type headache, and migraine with depression.
Serotonin Reuptake Inhibitors

Many patients prefer specific serotonin reuptake inhibitors (SSRIs) such as fluoxetine and sertraline. The less sedating effect of these medications make them attractive. They have not clearly been shown to have any antimigraine effect; however, they are good adjuncts in the treatment of migraine, especially in patients who cannot tolerate tricyclic antidepressants or experience unpleasant side effects.

Occasionally there can be a complication referred to as serotonin syndrome in patients who are on SSRIs, lithium, or monoamine oxidases and also receive 5-HT\textsubscript{1} agonists such as sumatriptan and DHE for acute attacks. We recently reported six patients with such a syndrome [41]. The manifestations of the syndrome consist of a combination of acute mental changes and neurological symptoms that include motor weakness, incoordination, myoclonus, and hyperreflexia. There may also be autonomic symptoms such as increased sweating, tachycardia, and fever. These are usually transient phenomena that occur in close proximity to the intake of the acute abortive agent. The recovery is complete. An increase in the available serotonin at the central synapses is thought to be the cause of this syndrome.

Calcium Channel Blockers

There are no good, adequately controlled studies on calcium channel blockers; however, many physicians with long-term experience find calcium channel blockers such as verapamil useful, especially in patients with complicated migraine (migraine with neurological symptoms such as basilar or hemiplegic migraine). Verapamil does cause water retention and constipation and should be used with care in patients with cardiac disorders. Verapamil is, of course, the most useful for the prophylaxis of cluster headache.

Serotonin Antagonists

Methysergide (Sansert) is probably the most effective medication for the prophylaxis of migraine. Seventy percent of patients benefit from it, usually with doses of about 6–8 mg daily. The immediate side effects include muscle pains in the leg, water retention, swelling, discoloration, and telangiectasia of the ankle area. The most worrisome side effects are fibrotic reactions, which may occur in the retroperitoneal or pulmonary tissue or in the cardiac valves. The overall incidence of fibrotic reactions is very low. It appears that this is an idiosyncratic reaction and does not have any relation to the dose used or the length of treatment. However, the FDA has special instructions for using methysergide, which include a drug holiday for 2 months after 6 months of use. Patients who receive repeated courses of methysergide, have to be monitored carefully with chest x-ray, echocardiogram, and computed tomography (CT) of the abdomen to rule out fibrotic reactions. Very rarely, renal failure occurs without any warning; therefore, these patients have to be followed carefully.

Cyproheptadine

Cyproheptadine is useful for children, especially young children, with migraine. Four milligrams three or four times a day is the dose in children; weight gain is sometimes a problem, and drowsiness may occur.

Divalproex Sodium in the Prophylaxis of Migraine

Divalproex sodium (valproic acid) is the latest addition to the armamentarium of drugs for the prophylaxis of migraine. Sodium valproate has been shown to reduce the neurogenic inflammation in Moskowitz’s experimental model [42].
It also has been shown to cause attenuation of c-fos activation in the trigeminal nucleus caudalis in Moskowitz’s experimental animals [43]. Valproate is known to increase gamma-aminobutyric acid (GABA) levels in the brain. In four separate double-blind studies, sodium valproate and divalproex sodium were shown to be superior to placebo [44–47]. Divalproex sodium also has been shown to be as effective as propranolol [48].

Divalproex sodium usually is given in small doses to start with, such as a 250-mg tablet twice a day, to be increased to a total of 1,000–1,500 mg per day. Starting with small doses and gradually increasing them in smaller increments will prevent the excess nausea and vomiting that may occur in some patients. The side effects of sodium valproate include asthenia, weight gain, hair loss, and tremor. Patients show an all-or-none response to valproate. Those who respond, respond very well and remain responsive for long periods. There is no point continuing the medication in those who do not show any response in a few weeks. Divalproex sodium is the only approved drug for migraine prophylaxis that has no direct cardiovascular effects. It can be used as a second-line drug in many patients and a first-line drug in the prophylactic treatment in the following situations:

1. When beta blockers are contraindicated, as in asthma, congestive cardiac failure, low blood pressure, cardiac conduction defects, depression, patients with immunotherapy for allergies who cannot take beta blockers, patients who cannot tolerate exercise intolerance on beta blockers
2. When the patient has comorbid migraine and epilepsy
3. When the patient has comorbid migraine and bipolar illness

It should be noted that valproate has been approved for use in bipolar illness as well as epilepsy and will soon be available for migraine prophylaxis.

### Prioritization of Prophylactic Pharmacotherapy

*Table 146-9* is a summary that helps to prioritize prophylactic migraine therapy. Clinical efficacy, scientific proof of efficacy, and side effect potential are graded from + to ++++, with ++++ being the highest grade. This is an empirical grading based on a review of the literature and the experience of the authors and is modified from Tfelt-Hansen and Welch [49].

The beta blockers methysergide and valproate are the most effective. One has to choose between them on the basis of their side effect potentials. Because the side effect potential of methysergide is high, it is not considered a first-line drug. On the basis of this assessment, beta blockers and valproate are more or less equal in performance.

### Continuity of Care

Patients with migraine need continuity of care. Tachyphylaxis to medications is possible; therefore, if the effectiveness diminishes, a change has to be made to another suitable medication. Side effects have to be monitored, and drug interactions must be kept in mind.

Comorbid conditions such as depression, anxiety, and neurotic behavior have to be treated with medications as well as with nonpharmacological approaches. Stress management, biofeedback therapy, and individual counseling may help in some patients.

### Treatment of Cluster Headache

#### Abortive Treatment of Acute Attacks of Cluster Headache

In the treatment of an acute attack of cluster headache, oxygen is the preferred agent [50].
Oxygen inhalation at 8 L/min for 10 min using a mask will abort the attacks of cluster headache in approximately 70% of patients. Our patients with cluster headaches rent portable oxygen tanks. Oxygen may simply delay the headache in some patients; the headache will return after an hour or so.

Oxygen inhalation can be combined with ergotamine in a form that is absorbed very rapidly. Ergotamine inhalation, which results in rapid plasma peak levels, is no longer available; therefore, one has to rely on sublingual, suppository, or oral preparations. Plasma peak levels after oral administration take longer time to achieve in acute attacks of cluster headache. Sublingual preparations are erratic in their absorption pattern and thus are not very reliable. Suppositories are inconvenient for administration in cases of cluster headache, which comes on rapidly without any warning and ceases rapidly. In spite of these disadvantages, some patients respond to a combination of oxygen and ergotamine in an oral, sublingual, or rectal form. One-milligram ergotamine tablets, 2-mg sublingual tablets, or 2-mg suppositories may be tried.

Sumatriptan is the drug of choice for acute episodes of cluster headache [51–53]. It is available in 100-mg tablets and 6-mg subcutaneous preparations. Subcutaneous sumatriptan produces a dramatic effect within 15 min of administration. It also can be combined with oxygen.
With this combination, the patient should get relief almost immediately and acute attacks should be aborted totally. Repeat administration of sumatriptan is possible, and the drug has not led to tolerance even after repeated use for more than approximately a year in patients with chronic cluster headache. Injectable sumatriptan is available in an autoinjector form and is very easy for patients to self-administer. The advantage of sumatriptan is its rapidity of action. Lack of nausea and vomiting is also a distinct advantage, as it is a specific 5-HT\textsubscript{1D} agonist without any effects on other neurotransmitter receptors.

Upper chest discomfort, a burning sensation at the site of injection, and a hot feeling in the body for a short period are the relatively minor side effects of sumatriptan. As the majority of patients with cluster headache are men and usually are heavy smokers, cardiac status has to be evaluated before drug therapy is started. Sumatriptan and ergotamine should not be used in patients with proven coronary artery disease and those who have multiple risk factors for coronary heart disease. Appropriate investigations to exclude ischemic heart disease have to be done before ergotamine, sumatriptan, and DHE are prescribed.

DHE administered intramuscularly relieves cluster headache attacks effectively but acts more slowly than does sumatriptan. Since cluster headache occurs one to three times a day on an average, repeated intramuscular injections are painful and impractical. A nasal spray of DHE is under trial.

Analgesics and narcotics have no real place in the treatment of cluster headache. It should be noted that the total period of pain from each cluster headache is approximately 45 min and that by the time an oral narcotic is absorbed and takes effect, the pain is usually over. The prescription of narcotic medications will simply lead to excessive use and habituation without any major benefit in terms of pain relief. Combination analgesics containing barbiturate and caffeine (Fiorinal preparations) have no place in the treatment of acute cluster headaches.

**Prophylactic Treatment of Cluster Headache**

Table 146-10 lists the medications used for the prophylactic treatment of cluster headache.

**Verapamil**

Among all the medications used for the prophylaxis of cluster headache, verapamil (Calan, Isoptin, Veralen) appears to be the most effective and is the drug of choice. The usual dose is 120 mg three to four times a day, but the dose may have to be increased in some patients. Verapamil should be continued for at least 2–3 weeks after the patient becomes totally free of headaches of the episodic variety. In chronic cluster headache, the length of treatment has to be determined by trial-and-error. Most patients with chronic cluster headache require verapamil for an indefinite period.
**Ergotamine**

Combinations of ergotamine and verapamil are known to produce very good results in patients with cluster headache. The dose of ergotamine is 1 mg twice a day, and unlike in migraine, its use in cluster headache does not appear to result in rebound phenomena. However, caution is necessary concerning daily ergotamine use in patients with risk factors for cardiovascular disease. Most cluster headache patients are heavy smokers, and some have hypertension; therefore, these patients have an increased risk for vascular disease.

**Lithium Carbonate**

Lithium carbonate is useful for both episodic and chronic cluster headache prophylaxis. Lithium is administered in divided doses of 300 mg two to three times a day. Lithium becomes effective in less than a week. If it is to be continued, monitoring of the lithium level to keep it in the low therapeutic range of about 0.5–0.6 mEq per liter is necessary. The plasma level of lithium should never exceed 1.2 mEq per liter. Lithium is reasonably well tolerated by most patients. While on lithium, these patients should not take sodium-depleting diuretics, as hyponatremia leads to lithium toxicity. The common side effects of lithium include nausea, vomiting, tremor, and lethargy. Neurotoxicity occurs at higher plasma levels, resulting in ataxia, blurred vision, confusion, and altered consciousness. Lithium can be combined with verapamil or ergotamine tartrate. Combinations of lithium and verapamil are the drugs of choice in the treatment of chronic cluster headache.

**Methysergide**

Methysergide is useful in patients with episodic cluster headache, whereas patients with chronic cluster headache are less responsive to it. One tablet (2 mg) three to four times a day is the standard dose. The side effects of methysergide are described in the section on the treatment of migraine, above.

**Corticosteroids**

Corticosteroids, particularly prednisone, have a definite place in the prophylactic treatment of cluster headache. The effect is usually dramatic, and these patients stop having cluster headache attacks within a day or two. However, when the corticosteroids are discontinued, the headache may recur with the original frequency. Because of exacerbation after the discontinuation of prednisone and the possibility of hypercorticism developing after frequent and prolonged use, prednisone should be reserved for short courses to break the cycle of headache when agents such as verapamil, ergotamine, lithium, and methysergide are not helpful. The usual dose of prednisone is 20 mg two to three times a day to start with, reduced gradually over a period of 2–3 weeks and then discontinued. The mechanism of action of corticosteroids in cluster headache is not clear; they may suppress the synthesis or release of humoral agents that mediate an attack of cluster headache or may influence neurotransmitters involved in the headache. Corticosteroids modulate serotonergic pathways in the brain and may affect the hypothalamic biological clock that is disrupted in patients with cluster headache.

Some headache specialists use prednisone at the onset of the cluster period along with verapamil. Then the prednisone is tapered off after 2 weeks, and the verapamil is continued for the duration of the cluster period. This is a reasonable alternative approach; however, as was mentioned above, exacerbation of the headache can occur after prednisone is discontinued, even though the chance of that happening is lower when the patients are continued on verapamil.
Indomethacin

Indomethacin is specific for and always successful in the treatment of chronic paroxysmal hemicrania, which is a variant of cluster headache that occurs mostly in women. The attacks are short-lived, lasting on average 5–10 min, as opposed to cluster headache, which lasts for 45 min to an hour. Multiple attacks (15–20 per day) occur, and autonomic symptoms may accompany the headache. The headache is always unilateral, and there are no remissions, resembling the pattern seen in chronic cluster headache. The therapeutic response to indomethacin can be used as a diagnostic test for chronic paroxysmal hemicrania. The usual dose of indomethacin is 25–50 mg three times a day. As with other NSAIDs, gastric side effects are common with indomethacin. Misoprostol (Cytotec) may help protect the upper GI tract from the effects of indomethacin in patients with chronic paroxysmal hemicrania who need to continue indomethacin for an indefinite period. Those on long-term indomethacin (Indocin) should have renal function tests periodically.

Beta Blockers and Antidepressants

Some of the medications that have been proved to be effective in the prophylaxis of migraine, such as beta-adrenergic blocking agents and tricyclic antidepressants, are not particularly useful in the treatment of cluster headache. However, an occasional patient may respond to these medications. In patients with chronic cluster headache who are also depressed, antidepressants may be of value as an adjunct.

Dihydroergotamine

DHE is useful in breaking the cycle of headache in those with intractable cluster headache attacks that do not respond to regular prophylactic therapy. DHE given intravenously every 6 h will invariably break the cycle in 2–3 days. The remission obtained with DHE gives the physician an opportunity to adjust the prophylactic therapy. A course of DHE may put a patient into remission for a considerable period.

Surgical Treatment of Chronic Intractable Cluster Headache

Approximately 10% of cluster headaches are chronic. By definition, chronic cluster headache patients have no remission of their headaches for at least a year. The headaches occur more frequently than in the episodic variety and are more difficult to treat medically. Prophylactic medical therapy includes combinations of agents such as verapamil, lithium, ergotamine, methysergide, and valproate and occasional short courses of corticosteroids. Triple therapy using any three of these agents may be the last pharmacotherapeutic strategy in some chronic cluster headache patients. When adequate trials of medical therapy fail completely, surgical treatment may be considered.

Indications for Surgery in Chronic Cluster Headache

There are several indications for surgery in chronic cluster headache patients:

1. Total resistance to medical treatment
2. Strictly unilateral cases
3. Stable psychological and personality profiles, including low proneness to addiction

Over the last few decades, a number of procedures have been tried for the surgical treatment of cluster headache (Table 146-11).
Radiofrequency Trigeminal Rhizotomy

Among the procedures listed in Table 146-11, those directed toward the trigeminal nerve, particularly percutaneous radiofrequency trigeminal rhizotomy, have been the most effective.\(^{[54-59]}\) Radiofrequency trigeminal rhizotomy utilizes thermocoagulation of the pain-carrying fibers of the trigeminal nerve. It is a stereotactic procedure. A needle is advanced through the foramen ovale under light general anesthesia. Once the needle is in place in the trigeminal ganglion region, the needle tip can be placed selectively, guided by electrical stimulation, in the individual V1, V2, or V3 roots of the sensory trigeminal nerve. Radiofrequency current is passed to the area of interest producing thermocoagulation and resulting in selective destruction of the pain fibers but maintaining touch sensation.

Experience in many centers indicates that approximately 70–75% of patients benefit from radiofrequency trigeminal rhizotomy. In the majority, the cluster headache attacks stop. In a smaller percentage, there is substantial improvement with occasional mild episodes. The results are not completely satisfactory, however, with failure occurring in approximately 15% of patients, often for technical reasons.

Those with excellent and good results retain the improvement for a number of years, and even long-term follow-up for more than 20 years has shown continuing benefit. However, recurrence of pain occurs in approximately 20% of those who initially had excellent or very good results, in which case surgery can be repeated. The recurrence may occur on the opposite side of the head; in our experience, patients with a history of occasional headache on the opposite side may be the candidates to develop significant recurrence on the opposite side. Therefore, we recommend selecting patients with a strictly unilateral history of headache.

A number of relatively minor complications can occur, especially in the immediate postoperative period, including transient diplopia, stabbing pain in the distribution of the trigeminal nerve, difficulty in chewing on the side of the lesion, and jaw deviation. These complications are usually transient, and complete recovery is the rule. A more troublesome complication is anesthesia dolorosa, although its incidence is very low. In our series of 98 patients with long-term follow-up, only 2 had moderately severe anesthesia dolorosa symptoms. Corneal analgesia may be produced by the radiofrequency lesion, in which case the patients have to be instructed to take particular care of their eyes after surgery and to consult an ophthalmologist if there is any sign of corneal infection. Untreated corneal infections can easily result in corneal opacification because of a lack of corneal sensation. The beneficial effects of this procedure, however, far outweigh the complications.

Some Observations

Some of our observations over the last 13 years in 98 patients who have received radiofrequency lesions are as follows:

1. Complete analgesia is necessary to ensure adequate beneficial effects. By comparison,
in trigeminal neuralgia, partial analgesia is all that is required

2. If the pain is confined to the orbital, retro-orbital, infraorbital, or supraorbital area, a lesion involving the V1 and V2 divisions of the trigeminal nerve is adequate. If the pain also occurs in the temples and in the area of the ear, a lesion of the third division is necessary because the auricular branch of the mandibular nerve supplies the temples and the ear.

**Retrogasserian Glycerol Injection**

Retrogasserian glycerol injection was once a popular procedure [59,60]. The disadvantages of this technique, however, are as follows:

1. Analgesia is, at most, not as complete as with radiofrequency lesioning
2. It is difficult to control the glycerol lesion, whereas with radiofrequency lesions, selective destruction of V1, V2, or V3 is possible
3. Glycerol may seep outside of Meckel’s cave and cause chemical meningitis

Many authors with experience with both radiofrequency lesions and glycerol injections prefer the former procedure.

In summary, surgical treatment of cluster headache is a last resort and should be restricted to patients with medically resistant disabling chronic cluster headache. Radiofrequency trigeminal rhizotomy is the surgical treatment of choice. In view of the disability and suffering of chronic cluster headache patients, the benefits of this procedure far outweigh the complications.

**References**


56. Sweet WH, Wepsic JG. Controlled thermocoaulation of trigeminal ganglion and rootlets for differential


