



# Pharmacology and use of headache medications

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■ Treatment of headache disorders is most likely to be successful when the pathophysiology of the disease is correlated with the pharmacologic actions of the available drugs. Beta blockers generally are considered first-line therapy for migraine prophylaxis, but calcium blockers also are appropriate for some patients. Antidepressants are the primary modality for treatment of tension type headaches, although they are also used for migraine prophylaxis. Mixed headache, which has features of both migraine and tension-type headache, usually requires treatment with more than one drug. Habituation to analgesics is common among patients with mixed headache.

□ INDEX TERM: HEADACHE □ CLEVE CLIN J MED 1990; 57:627-635

**M**OST DRUGS indicated for the treatment of headache disorders are safe and effective when used appropriately. The key to successful management of headache is to individualize therapy as closely as possible to the patient's needs. This requires making an accurate clinical diagnosis,<sup>1-3</sup> understanding the pathophysiology of the disease, correlating the pharmacology of medications with the neurobiology of the specific headache type, and applying that knowledge to the patient with respect to concomitant illness and potential adverse effects.

## PATHOPHYSIOLOGY

The pathophysiology of headache remains unclear, with a blurred distinction between vascular and

neurogenic theories. Despite the uncertainties, some simple concepts help explain the behavior of headache patients and the actions of many headache medications.

## Migraine

Migraine is a complex disorder, involving the release of several neurotransmitters, platelet aggregation with release of platelet serotonin, and vasodilation of cerebral and extracerebral arteries. According to the vascular theory, based on the pioneering work of Wolff<sup>4</sup> and Graham,<sup>5</sup> migraine is a disorder of cerebrovascular regulation. The proposed sequence of events in migraine begins with the release of an as-yet-unidentified substance, possibly a neurotransmitter such as substance P, serotonin, or both. The release precipitates platelet aggregation, release of platelet serotonin, thromboxane A<sub>2</sub> activation of prostaglandins with production of kinins, and the production of a localized sterile arteritis that causes symptomatic focal vasoconstriction. Reactive vasodilation follows, largely in the extracranial cerebral circulation, stretching the pain-sensitive arterioles and producing the familiar throbbing headache of migraine.

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Studies by Lance,<sup>6</sup> Olesen,<sup>7</sup> Moskowitz,<sup>8</sup> and others have promoted the neurogenic theory of migraine. This work emphasizes the release of central nervous system neurotransmitters (substance P, serotonin) as the mediators of migraine symptoms and pain, with intracerebral vascular changes occurring as secondary events.

Recent work from our own laboratory<sup>9</sup> confirms that a fall in free plasma serotonin and an elevation in plasma substance P levels occur during an acute migraine attack. Lance<sup>10</sup> found that, even between attacks, migraine sufferers had lower serotonin levels than controls.

### Chronic tension-type headache

Chronic tension-type headache appears to be one of a group of disorders marked by decreased levels of serotonin. Other diseases in this group include fibrositis/fibromyalgia,<sup>11</sup> depression,<sup>12</sup> alcoholism,<sup>13</sup> and premenstrual syndrome (PMS).<sup>14</sup> Harvey and associates<sup>15</sup> found that in animals, serotonin depletion led to increased pain sensitivity and arousal. Patients with chronic tension-type headache also report increased pain sensitivity along with other symptoms, including constant headache, generalized myalgias and arthralgias, difficulty initiating or maintaining sleep, chronic fatigue, carbohydrate craving, decreased libido, irritability, and disturbed memory and concentration.

### Mixed headache

Although not defined by the International Headache Society's classification scheme,<sup>3</sup> mixed headache or evolved migraine constitutes most patients treated in specialized headache centers. Mixed headache syndrome is defined as daily or almost daily headache, with intermittent migraine attacks, and frequent, often excessive, analgesic use.<sup>16</sup> Many of these patients have a history of migraine onset in their teens or early twenties, and the development of daily headaches between the ages of 35 and 45. Patients with mixed headache generally present with other symptoms common to chronic tension-type headache, including sleep disturbances, depressed moods, carbohydrate craving, and memory and concentration problems. As in patients with chronic tension-type headache, mixed headache sufferers often have family histories that include alcoholism, sexual abuse, and depression.

One theory of the pathophysiology of the mixed headache syndrome proposes that these patients initially suffer with migraine headache, with acute drops in serotonin and chronically low levels of serotonin between attacks. Over several years, the level of serotonin

drops below a critical level and symptoms of serotonin depletion, such as mood changes, sleep disorders, carbohydrate craving, and decreased libido, emerge. Eventually, chronic tension-type headaches develop in these patients who already suffer from intermittent migraines.

Overuse of habituating analgesics appears to hasten this process—a scenario commonly observed in headache clinics. The data on serotonin levels need confirmation.

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### MIGRAINE PHARMACOLOGY

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The pharmacologic treatment of migraine may be either prophylactic or symptomatic (abortive). The decision to use daily medication as prevention is based on the frequency of attacks, inability to tolerate symptomatic medications, ineffectiveness of symptomatic medications, and most importantly, how significantly migraine impairs the patient's quality of life. Some experts suggest that patients with two or more migraines each month receive prophylactic therapy, but patients with less frequent attacks also may benefit, particularly if migraine causes frequent absences from work or interruption of family life.

Saper<sup>17</sup> lists five guidelines for selecting prophylactic rather than abortive treatment: (1) more than one or two headaches per week, (2) medical contraindications to symptomatic therapies, (3) failed symptomatic therapies, (4) regular and predictable attacks (eg, menstrual migraine), and (5) known substance abuse tendencies.

Because of abundant clinical experience, beta blockers are generally considered first-line therapy for prophylaxis. Calcium channel blockers, particularly verapamil in the United States and flunarizine (investigational in the United States) and nimodipine in Europe, are widely regarded as useful alternatives. Calcium channel blockers are appropriate for patients who have contraindications to beta blockers, are intolerant of beta blocker side effects, or respond poorly to beta blocker therapy. The nonsteroidal anti-inflammatory drugs (NSAIDs) are valuable either as first-line therapy or in combination with other prophylactic agents for difficult-to-manage patients. Although studies have not shown whether combination therapy is more effective than single-agent therapy, it is often used in clinical practice (Table 1).

Other modalities include anti-serotonin antihistaminic agents<sup>18</sup> and several drugs still in development or testing, such as angiotensin converting enzyme (ACE) inhibitors, 5-HT<sub>1</sub>-like receptor agonists, methyl donors, and opiate antagonists.

Drug selection is best based on consideration of concomitant illness, concurrent medications, blood pressure, evidence of depression or sleep disorder, and experience with prior medication.

Patients with migraine and concomitant hypertension will benefit from treatment with a beta blocker, calcium channel blocker, or ACE inhibitor, while those patients with low blood pressure may be better candidates for NSAID therapy.<sup>19</sup> Patients with depression should not be given beta blockers, but they may benefit from antidepressants or ACE inhibitors.<sup>19</sup> Drug interactions may be dangerous in patients taking monamine oxidase inhibitors, and they must be considered in any patient taking multiple medications.

Although methysergide is considered by many to be one of the most effective prophylactic agents available, it is generally reserved for patients in whom all other therapies have failed. The drug has a small risk of serious adverse effects.

### Beta blockers

Several beta blockers are effective for migraine prophylaxis, but propranolol is the only one approved by the Food and Drug Administration (FDA) for this indication. Propranolol is a nonselective beta blocker with high lipophilicity and membrane-stabilizing activity with confirmed efficacy and safety.

Long-acting propranolol has also been found effective for migraine prophylaxis, and is more convenient than a multiple-dose regimen. In a study of 80 unselected patients referred to a specialized headache clinic and treated with long-acting propranolol alone,<sup>20</sup> 64% had a good or excellent outcome—results comparable to those observed with regular propranolol. A once-daily dose of 60 mg to 80 mg is usually effective, although an occasional patient may require a higher dose.

Propranolol and the other nonselective beta blockers,

**TABLE 1**  
CHARACTERISTICS OF SELECTED MIGRAINE TREATMENTS

Drug	Use	Dosage	Comments
Propranolol (long-acting)	Prophylaxis	60-80 mg/d	Nonselective beta blockers considered more effective than selective beta-1 blockers
Verapamil	Prophylaxis	320-360 mg/d	Clinical effect becomes evident after about 4 wk; other calcium blockers also effective, but verapamil used most commonly
Naproxen	Prophylaxis	375-500 mg bid	
Naproxen sodium	Abortive therapy	825 mg followed 30 min later by 275 mg if needed	
Fenoprofen	Prophylaxis	600 mg tid	
Mefenamic acid	Menstrual migraine prophylaxis	250 mg bid or tid beginning 3 d prior to onset of and continuing through menses	
Captopril	Prophylaxis; adjunct to tricyclics in tension-type and mixed headaches	50 mg tid	Preliminary data are encouraging, but no large trials completed
Cyproheptadine	Prophylaxis	Children: 4 mg mg bid or tid; adults: 12-32 mg/d in divided doses	Considered useful for children; troublesome side effects in adults
Estradiol	Menstrual migraine prophylaxis	1-5 mg/d for 7 d starting 48 hr before onset	Percutaneous formulation

nadolol and timolol, are thought to be more effective than selective beta<sub>1</sub> (cardioselective) blockers.<sup>21</sup> The selective beta blockers atenolol and metoprolol also have been found to be effective for migraine prophylaxis. Beta blockers with intrinsic sympathomimetic activity have not been found useful in migraine prophylaxis.

The exact mechanism of action of beta blockers in migraine is unknown. It is known that these drugs block beta-receptors in vascular smooth muscle to prevent arterial dilation, inhibit catecholamine-induced platelet aggregation and platelet adhesiveness, and block catecholamine-induced lipolysis and prostaglandin production.<sup>22</sup> In addition, they inhibit forebrain postsynaptic serotonin receptors.

Beta blockers should be avoided in patients with asthma, congestive heart failure, or atrioventricular conduction disturbances, and used with caution in insulin-dependent diabetics and patients with depression or sleep disturbances.

### Calcium channel blockers

The calcium channel blockers verapamil, diltiazem,

nifedipine, nimodipine, and flunarizine have been found effective in the prophylaxis of migraine.<sup>23</sup> In the United States, verapamil is the most commonly used calcium blocker for migraine. This drug is well tolerated, with constipation the only common side effect. Prophylactic verapamil therapy should be initiated at a daily dosage of 320 mg to 360 mg.<sup>24</sup> Both flunarizine and nimodipine are more selective for the cerebral vasculature than peripheral blood vessels when compared with verapamil, diltiazem, and nifedipine. In addition to constipation with verapamil, other common side effects of the calcium channel blockers include sedation and weight gain with flunarizine; flushing, edema, and increased headache with nifedipine; and gastrointestinal upset with diltiazem. With most calcium channel blockers, there appears to be a delay of about 4 weeks before significant improvement is reported; therefore, therapy should be continued for at least 8 weeks to ensure an adequate therapeutic trial. Like beta blockers, these drugs are contraindicated in patients with congestive heart failure or atrioventricular conduction disturbances, but are safe in patients with asthma.

The drugs in this class work by blocking arterial vasoconstriction (with resulting rebound vasodilation), inhibiting platelet serotonin uptake and release, and augmenting cerebral blood flow.

### Nonsteroidal anti-inflammatory drugs

Several nonsteroidal anti-inflammatory drugs have prophylactic activity in migraine. Among these are aspirin,<sup>25</sup> flufenamic acid,<sup>26</sup> tolfenamic acid,<sup>27</sup> fenopropfen calcium,<sup>28</sup> naproxen,<sup>29-31</sup> and ketoprofen.<sup>32</sup>

The effects of NSAIDs on platelets may explain their efficacy in migraine prophylaxis. NSAIDs prevent platelet aggregability and serotonin release. Platelet activity in migraine patients differs from that of controls, with chronic aggregation and significant increases in platelet adhesiveness during the headache phase of migraine. The aggregated platelets release vasoactive prostaglandins and serotonin.<sup>33,34</sup> These changes are responsible for the increased level of plasma serotonin during the headache prodrome and the subsequent decrease during the headache phase. Prostaglandin E<sub>1</sub> causes dilation of the external carotid arteries, while prostaglandin F<sub>2</sub> induces intracerebral vasoconstriction.<sup>35</sup>

Nonsteroidal anti-inflammatory drugs act to inhibit inflammation through their effects on chemotaxis, phagocytosis, lysosomal enzyme release, kinin generation, complement generation, and formation of prostaglandins.<sup>36</sup>

Naproxen is a propionic acid derivative with analgesic, anti-inflammatory, and antipyretic properties. It is completely absorbed after oral administration, achieving therapeutic serum concentrations after 20 to 30 minutes, and maximum concentration after 2 hours. Its biological half-life is 12 to 15 hours.<sup>29</sup> The sodium salt of naproxen, naproxen sodium, is more rapidly absorbed than naproxen, producing earlier and higher plasma levels.<sup>37</sup> Because of these differences, naproxen is often chosen for prophylactic use, while naproxen sodium has been used as both an abortive<sup>38,39</sup> and a prophylactic agent.<sup>40</sup>

The usual naproxen dosage for migraine prophylaxis is 375 mg to 500 mg twice daily; the dosage for naproxen sodium is 550 mg twice daily. The usual dosage for abortive therapy is 825 mg of naproxen sodium, followed by 275 mg in 30 minutes, if needed.<sup>38</sup>

Like naproxen, *fenopropfen calcium* is a propionic acid derivative with analgesic, anti-inflammatory, and antipyretic properties that is effective in migraine prophylaxis.<sup>28</sup> Compared to placebo, fenopropfen significantly reduced migraine frequency. With a regimen of 600 mg three times daily, it also significantly reduced the severity and duration of migraine attacks.

Work is currently being conducted with *flurbiprofen*, 100 mg twice daily, for migraine prophylaxis. Preliminary clinical experience with this drug suggests a high degree of efficacy and patient tolerance.

*Mefenamic acid*, 250 mg two or three times daily, is used to prevent menstrual migraine. The patient begins treatment 3 days prior to onset of menses and continues through menses.<sup>21</sup>

One of the significant advantages of nonsteroidal anti-inflammatory drugs is the absence of cardiovascular effects. NSAIDs may be used safely in patients with underlying cardiac disease, where beta blockers or calcium channel blockers might be contraindicated. Additionally, unlike beta blockers and some calcium channel blockers, nonsteroidal anti-inflammatory drugs do not lower blood pressure. These qualities allow this class of drugs to be used in combination with most other migraine prophylactic agents.

The most common adverse effect is gastric upset. Other side effects may include light-headedness, fatigue, and edema.

### Angiotensin-converting enzyme inhibitors

The angiotensin-converting enzyme (ACE) inhibitors may have value in migraine prophylaxis. Captopril has been reported to inhibit the enzyme enkephalinase, blocking the breakdown of the naturally occurring opiate, enkephalin. Opiates inhibit the release



of substance P from primary sensory neurons. Substance P induces vasodilation, plasma extravasation, nasal and conjunctival congestion, and may take part in nociceptive transmission within the trigeminal system.

Although there are no large studies of ACE inhibitors in migraine, preliminary experience with these drugs is encouraging. Minervini<sup>41</sup> studied 12 patients with both classical migraine and endogenous depression. After treatment with captopril, 50 mg three times daily, all 12 patients had more than 50% improvement in migraine index, 8 were headache-free, and 9 had significant attenuation of depressive symptoms. The only significant side effect reported was hypotension.

Sicuteri<sup>42</sup> evaluated 35 patients in an uncontrolled trial and found significant benefit in 23 of 35 patients (including 11 of 11 with hypertension and migraine). Captopril may also be a beneficial adjunct to tricyclic therapy in patients with chronic tension-type headache and mixed headache syndrome.

### Methysergide

Methysergide, a lysergic acid derivative closely related to the ergot alkaloids, has been used in migraine prophylaxis since the work of Sicuteri<sup>43</sup> in 1959, and Freidman and Elkind<sup>44</sup> in the early 1960s. It inhibits the vasoconstrictor and pressor effects of serotonin (5-HT),<sup>45</sup> but potentiates the vasoconstrictor effects of norepinephrine.<sup>46</sup> Unlike lysergic acid, methysergide has little effect on the nervous system.<sup>45</sup>

The mechanism of action of methysergide is uncertain. It may reduce the pain-producing effect of serotonin that is released from platelets and absorbed by the vessel walls; it may reduce the vasoconstrictor activity of serotonin on small arteries; it may maintain tonic vasoconstriction of large arteries once the serotonin level has fallen; or the mode of action may be unknown.<sup>46</sup>

Lance and colleagues<sup>47,48</sup> pronounced methysergide the most useful agent for migraine prophylaxis; they found that a dosage of 2 mg to 6 mg per day suppressed migraine completely in 26% of patients and substantially improved an additional 40%. Side effects, predominantly abdominal discomfort and muscle cramps, were reported in about 40% of patients, but were usually transient.

The major deterrent to the use of methysergide is the potential for retroperitoneal, cardiac, and pulmonary fibrosis. This effect is rare; the highest reported incidence is 1% in patients treated continuously.<sup>49</sup> The fibrosis usually regresses after discontinuation of the drug, but permanent fibrotic changes have been reported.<sup>45</sup>

To reduce the likelihood of this potentially fatal side effect, methysergide should be discontinued for at least 4 weeks every 6 months,<sup>50</sup> and patients should be evaluated regularly during treatment with intravenous pyelography, chest radiographs, and electrocardiograms. Peripheral vasoconstriction and limb claudication can occur if the daily dose exceeds 8 mg.<sup>51</sup> Because of the serious potential problems with this agent, the marked increase in migraine frequency during "drug holidays," and the availability of other agents, methysergide should be used rarely for migraine prophylaxis.

### Cyproheptadine

Cyproheptadine has serotonin antagonist effects similar to those of methysergide, but also is an active histamine H<sub>1</sub> antagonist. In addition, it has weak anticholinergic activity and mild central depressant properties.<sup>45</sup> Despite few controlled trials of this drug for the treatment of headache,<sup>18</sup> Saper<sup>17</sup> considers it to be the drug of choice in children.

The usual dosage for children is 4 mg two to three times daily. In adults, the usual dosage ranges from 12 mg to 32 mg daily in divided doses. The drug is not commonly prescribed for adults because of its modest success in adulthood and because the major side effects—sedation, appetite stimulation, weight gain, dry mouth, and constipation—tend to be tolerated less in adults. Cyproheptadine has not been approved by the FDA for treatment of headache.

### Fish oil

Omega-3 fatty acids in high doses can inhibit prostaglandin synthesis and reduce platelet serotonin release.<sup>52</sup> Glueck and colleagues<sup>52</sup> studied 15 migraine patients in a double-blind, placebo-controlled trial of omega-3 fatty acids, 15 g per day. They reported a statistically significant improvement in headache intensity, but they did not report on headache frequency. Because this work was published only in abstract form, it is difficult to evaluate the overall efficacy of this treatment. Furthermore, the dosing of fish oil requires 15 capsules per day, making it both expensive and impractical.

### Estrogens and estrogen antagonists

Menstrual migraine remains one of the most difficult of all headache disorders to treat. The physiologic withdrawal of estrogens during the premenstrual phase has been suggested as the precipitating event leading to migraine.<sup>53</sup> In one study that explored this idea, 18 women with menstrual migraine and regular menstrual cycles were treated with percutaneous estradiol, 1 mg to

5 mg per day, for 7 days each month starting 48 hours before the expected onset of migraine.<sup>54</sup> When compared with placebo, menstrual attacks occurred significantly less often (31% of cycles *v* 96% of cycles), and those that did occur were milder and shorter in duration. Only one patient developed a migraine after stopping the estradiol, but a few patients noted amenorrhea or changes in cycle duration. This report contrasts with the poor results seen with oral estrogen therapy.<sup>55</sup>

Tamoxifen, an anti-estrogen, may be effective for some women with migraine. Powles<sup>56</sup> reported on six women whose migraines were significantly improved while on tamoxifen, 20 mg daily. All of these patients were taking tamoxifen for benign mammary dysplasia. In three patients who discontinued tamoxifen, the headaches recurred within a few weeks. However, this work needs to be confirmed by a placebo-controlled study before tamoxifen is considered as a primary therapy for migraine.

### Opiate antagonists

Naltrexone, a long-acting oral congener of naloxone, was reported to yield marked improvement in two patients with postconcussion syndrome marked by severe headache, blackouts, and amnesia.<sup>57</sup> This paper did not describe the headaches in detail.

Many patients report the onset of migraine after head trauma; patients with pre-existing migraine note the dramatic worsening of their migraines after head trauma. Naloxone may offer an additional treatment option for the patient who suffers from refractory, post-traumatic headache.

### 5-HT<sub>1</sub>-like receptor agonists

Reportedly, 5-HT<sub>1</sub> agonists alleviate the pain and nausea of an acute migraine attack. This contrasts with prophylactic medications that block the reuptake of serotonin or antagonize the 5HT<sub>2</sub> receptor (methysergide). Sumatriptan<sup>58</sup> is a 5-HT<sub>1</sub> receptor agonist, currently under investigation, that should become available in both parenteral and oral dosage forms. While early data suggest that this drug may become a useful abortive agent, data are lacking on its use as a prophylactic medication.

### Dihydroergotamine

For many years, ergotamine tartrate has been considered the "gold standard" for abortive migraine therapy. Ergotism, a condition of peripheral vasospasm and gastrointestinal upset caused by ergotamine abuse, is not common, but ergotamine-induced rebound

headaches may be quite common in those patients who take ergot medications several times a week.<sup>59</sup> Long-term use of ergotamine therapy is associated with fibrotic processes (retroperitoneal, pulmonary, or pericardial fibrosis).<sup>60</sup>

Neuman and colleagues<sup>61</sup> evaluated the use of oral dihydroergotamine, 5 mg twice daily, in a study of 40 patients. Migraine frequency fell from 3.3 to 1.3 attacks per month in the treatment group, compared to 3.0 attacks per month with placebo ( $P < 0.001$ ). Ninety-five percent of patients noted some improvement with dihydroergotamine therapy. No side effects were reported.

Dihydroergotamine is unavailable in oral form in the United States. The only orally available ergot, ergotamine tartrate, causes significant rebound headache with daily use, and cannot be substituted for dihydroergotamine. Dihydroergotamine is available for parenteral use only, but a nasal spray may be marketed soon.

### Methyl donors

S-adenosylmethionine (SAM) is a methyl donor that acts as a co-substrate in the metabolism of serotonin and norepinephrine. SAM activates cerebral serotonin turnover and causes an increase in 5-HIAA concentrations in cerebrospinal fluid and plasma. In an Italian pilot study,<sup>62</sup> 124 patients were treated with a 2-hour intravenous infusion of 400 mg of SAM every morning for 30 days. Headache index was reduced significantly ( $P < 0.01$ ) as was the use of pain relievers. The need for daily intravenous administration makes this therapy untenable at present, but methyl donor therapy may have value if oral dosage forms become available.

### Antidepressants

The mechanism of action of antidepressants in migraine headache is uncertain. Raskin<sup>63</sup> states that the cardinal abnormality of migraine is the defective modulation of serotonin (5-HT) release, with intermittently reduced synaptic serotonin levels and secondarily increased dorsal raphe neuronal firing rates. Some antidepressants, such as trazodone and fluoxetine, selectively inhibit serotonin uptake in both brain and human platelets.<sup>63,64</sup> This may mediate both platelet activation and vasomotor regulation.<sup>63</sup> Chronic treatment with antidepressants decreases the density and changes the affinity of 5-HT<sub>1</sub>-receptor binding and reduces the number of 5HT<sub>2</sub>-receptors.<sup>65</sup>

Certain tricyclic antidepressants, such as amitriptyline, have calcium channel blocking properties<sup>66</sup> that may prevent vasoconstriction and cerebral hypoxemia.

## TREATING TENSION-TYPE HEADACHE

The treatment of tension-type headache is largely based on the concept of replacing serotonin and norepinephrine within the synapse. The primary therapy is antidepressant medication.

The antidepressants, particularly tricyclic agents such as amitriptyline, have been used in the treatment of tension-type headache and in the prophylaxis of migraine for a number of years.<sup>67</sup> These drugs are most useful in patients with tension-type headache, mixed headache syndrome, or in migraine patients with depressive features. Both tricyclics and monoamine oxidase inhibitors (MAOIs)<sup>68</sup> have been effective; however, tricyclics are generally the first choice because of their lower incidence of side effects and lower potential for serious drug interactions. This group includes amitriptyline, imipramine, trimipramine, doxepin, desipramine, protriptyline, nortriptyline, amoxapine, and the non-tricyclic, non-MAOIs maprotiline, trazodone, bupropion, and fluoxetine. The efficacy of these drugs has been shown in several studies.<sup>67-69</sup>

The choice of tricyclic depends on the unique characteristics of each agent. Drugs such as desipramine, protriptyline, bupropion, and fluoxetine are nonsedating, and are therefore preferred for patients without a sleep disorder. Furthermore, fluoxetine and bupropion have minimal anticholinergic effects and may cause weight reduction. Of the sedating tricyclic drugs, trazodone has minimal anticholinergic effects and does not commonly cause weight gain.

Patients with symptoms of serotonin depletion (generalized myalgias and arthralgias, difficulty initiating or maintaining sleep, chronic fatigue, carbohydrate craving, decreased libido, irritability, and disturbed memory and concentration) respond better to fluoxetine, a serotonin reuptake inhibitor, than do patients who have chronic daily headache, but without associated symptoms. Patients without symptoms of serotonin depletion may respond better to traditional tricyclic antidepressants. Women with chronic daily headaches and premenstrual syndrome have had marked improvement in PMS symptoms during treatment with fluoxetine.<sup>69</sup>

Alprazolam, a benzodiazepine with antidepressant effects, may have efficacy in migraine headaches. Othmer and colleagues<sup>70</sup> reported on one patient with refractory migraine and depression who was included in a placebo-controlled, double-blind trial with alprazolam. This patient responded to alprazolam, 5 mg per day, with complete headache relief, but had no

response to placebo. Additional studies with larger numbers of patients will be needed to confirm this work.

Some patients with chronic tension-type headache will not respond to antidepressant therapy alone. Several adjunctive therapies have been proposed, including NSAIDs, ACE inhibitors, lithium, thyroxine, and direct stimulants (methylphenidate). Some headache experts use combinations of monoamine oxidase inhibitors and tricyclic antidepressants.

## TREATMENT OF MIXED HEADACHE

Because the mixed headache syndrome combines features of both migraine and tension-type headache, therapy with more than one medication is commonly required. Tricyclic antidepressants and NSAIDs can be effective for both migraine and tension-type headaches, making them appropriate for the initial treatment of mixed headache. When a single agent is ineffective, then antidepressants are usually prescribed in combination with migraine prophylactic drugs, such as calcium blockers, beta blockers, or NSAIDs.

Habituation to analgesics is a major feature of the mixed headache syndrome. Drugs commonly abused by patients with daily headaches include butalbital combinations, ergotamine, benzodiazepines, propoxyphene, codeine, and other opiates. Detoxification from habituating drugs is the most important step in the treatment of patients who use excessive habit-forming medications.

Prophylactic medications are ineffective in patients suffering from rebound or withdrawal headaches. Although patients commonly state that they "would stop taking painkillers if only the preventive drugs worked," the preventive drugs will never work as long as the patient is habituated to analgesics.

Few data have accumulated on detoxification of the headache patient. Patients who are addicted to narcotics can benefit from the use of clonidine to prevent withdrawal symptoms. At the Cleveland Clinic, corticosteroids and phenothiazines are prescribed for outpatient detoxification from butalbital, ergotamine, or low doses of narcotics. Generally, a 10- to 14-day tapered course of prednisone is given, with chlorpromazine suppositories prescribed for severe withdrawal headaches. Prophylactic medications are usually started at the time of detoxification, but, because the quality and frequency of headaches are often different after successful detoxification, the choice of medication may change.



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