If Only you Could Feel my Pain— the Anguish of Migraine

Shanan Brinson Muñoz, MD

Various descriptions and works of art have attempted to convey the misery of migraine. It is a common cause of disabling headache, especially in women, and can interfere with one's total life: career, family, and social. Headache is the leading cause of absenteeism from work, and even if the sufferer goes to work with a migraine, she is less productive. She may feel guilty for being unable to fulfill responsibilities and for being irritable. Children may fear their "Migraine Mom" who looks sickly, lying in a dark room popping pills, injecting medicines, and angrily refusing to read stories or play games. During these times, older children may need to care for younger ones. If the patient needs to go to the emergency room, she has to arrange for someone to watch her children and for someone else to drive her. Patients lament if their children have inherited migraines from them. Furthermore, society views migraines as an invalid illness, considering the individual to be frail or a complainer. This may explain why only 15% to 30% of people with migraine see a physician each year. Patients need to feel confident that their physicians will understand their pain and properly diagnose them. When migraine is diagnosed correctly, its presentations, pathogenesis, triggers, and treatments can be explained, and patients can be helped to return to their many roles in life.

A devasting headache as depicted by George Cruikshank, 18th Century English engraver and humorist. Courtesy of the Bettmann Archive, New York City.

Because headaches often are misunderstood, they frequently are misdiagnosed and mistreated. The International Headache Society (IHS) Headache Classification describes 13 headache types and more than 10 subdivisions. Headaches can be divided into primary or secondary, with the latter being symptomatic of an underlying medical condition (ie, a tumor). The most common headaches are primary and include migraine, tension-type, and cluster.

Migraine is divided into seven major divisions with subdivisions (See Table 1). Migraine without aura (MO), or common migraine, is found in 80% to 85% of those with migraine. The diagnostic criteria are listed in Table 2. Many patients have migraine both with and without aura. The criteria for migraine with aura (MWA), or classic migraine, are listed in Table 3.

The most common aura is visual, such as brief flashes of light (photopsia) or multicolored jagged shapes ("fortification" spectra). Some patients experience a "scotoma," or a small black area in their visual fields, or even homonymous hemianopsia. Next in frequency are sensory disturbances, with dysphasias and hemiparesis occurring less often. Auras may consist of one or more symptoms and usually last 20 to 30 minutes, preceding headaches by 5 to 60 minutes. Their cause is unclear, with theories proposing neurochemical, electrical, or vasoconstriction etiologies or combinations of these. (See Illustration.)

Migraine with prolonged aura has one or more symptoms lasting longer than 1 hour but fewer than 8 days with normal neuroimaging. Familial hemiplegic migraine has an aura that includes hemiparesis and may be prolonged; at least one first-degree relative has had identical attacks. Migraine aura without headache is common in patients with MWA but less common in patients without a history of migraine.

A particularly disturbing variant of migraine is basilar migraine, which occurs primarily in adolescent girls, results from ischemia within the basilar

Shanan Brinson Muñoz, MD, Dallas Neurological Associates.

Table 1.—Seven Types of Migraine

- Migraine without aura
- Migraine with aura
  - Migraine with typical aura
  - Migraine with prolonged aura
  - Familial hemiplegic migraine
  - Basilar migraine
  - Migraine aura without headache
  - Migraine with acute onset aura
- Ophthalmoplegic migraine
- Retinal migraine
- Childhood periodic syndromes that may be precursors to or associated with migraine
  - Benign paroxysmal vertigo of childhood
  - Alternating hemiplegia of childhood
- Complications of migraine
  - Status migrainosus
  - Migrainous infarction
- Migrainous disorder not fulfilling above criteria

artery distribution, and has two or more of the following aura symptoms:

- Visual symptoms in both the temporal and nasal fields of both eyes
- Dysarthria
- Vertigo
- Tinnitus
- Decreased hearing
- Double vision
- Ataxia
- Bilateral paresthesia
- Bilateral paresis
- Decreased level of consciousness

There are several less common migraine types. Ophthalmoplegic migraine is associated with paresis of more than one ocular cranial nerve in the absence of demonstrated intracranial lesions. Retinal migraine has fully reversible monocular scotoma or blindness lasting less than 1 hour. A headache follows the visual symptoms less than an hour later, or it may precede them. Ophthalmologic exam outside of an attack is normal, and embolism must be ruled out. The childhood periodic syndromes may be precursors to or associated with migraines. They include Benign Paroxysmal Vertigo of Childhood, which consists of multiple, brief, sporadic episodes of disequilibrium, anxiety, and often nystagmus or vomiting with a normal neurologic exam and EEG. The other syndrome is Alternating Hemiplegia of Childhood, which has its onset by age 18 months and consists of repeated attacks of hemiplegia involving both sides of the body. Movement disorders, ocular motor abnormalities, and autonomic disturbances may occur with the hemiplegia or independently. There is evidence of mental or neurologic deficits.

Complications of migraine include status and infarction. Status migrainous is defined as a migraine lasting longer than 72 hours despite treatment. Headache-free intervals of less than 4 hours, excluding sleep, may occur. Migrainous infarction consists of an attack typical of prior attacks, but the neurologic deficits are not completely reversible within 7 days and/or neuroimaging demonstrates an ischemic infarct in a relevant area. Other causes of infarct must be ruled out.

In the American Migraine Study, questionnaires were mailed to 15,000 homes and completed by those with severe headaches. International Headache Society criteria was used, except the number of prior migraines and headache duration were not considered. Migraine prevalence was 17.6% for females (highest between ages 25 and 55) and 6% for males. It was estimated that 23 million US residents endure severe migraines. Twenty-five percent of females with migraine experienced four or more severe attacks per month and more than 85% had some disability from them, with one third being extremely disabled.[1]

PUBERTY AND HORMONES

Before puberty, migraine is more common in boys, but after puberty, girls have a higher prevalence. Women may have an increase in the severity and frequency of headaches perimenopausally and then a decrease after menopause. Increased incidence and severity of migraine occurs just before or during menses in 60% of females with migraine. Migraine occurs more frequently in those with irregular, painful menses and metrorrhagia. Some

Table 2.—Diagnostic Criteria of Migraines without Aura (MO)

A. Headaches which last 4 to 72 hours (untreated or unsuccessfully treated)

B. Headaches which have at least 2 of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe intensity
   4. Aggravation by walking stairs or similar routine physical activity

C. Headaches accompanied by at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and/or sonophobia

D. At least 5 headache attacks fulfilling A through C above

Table 3.—Diagnostic Criteria of Migraines with Aura (MWA)

A. Migraines with at least three of the following characteristics:

1. One or more fully reversible aura symptoms indicating local cerebral cortical and/or brainstem dysfunction
2. At least one aura symptom developing gradually over more than 4 minutes, or two or more symptoms occuring in succession
3. No aura symptom persisting more than 60 minutes; if more than one aura symptom is present, accepted duration is proportionally increased
4. Headache following aura with a free interval of less than 60 minutes (It also may begin before or with the aura.)

B. At least two attacks fulfilling A.

patients may have increased migraines at ovulation.

Oral contraceptives (OCP) cause an increase in attacks in 18% to 49% of females with migraine, with more headaches occurring during the drug-free interval of the cycle.[2] Headaches may improve by decreasing the dose, changing the estrogen type, or decycling. A fall in estrogen level is associated with attacks and helps explain menstrual migraine and why stable estrogen levels can prevent it. Headaches tend to increase in the first trimester of pregnancy, which may be a result of changing hormones. In the last trimester, a decrease occurs in the usual number of headaches in 75% of cases. Migraine may recur postpartum but may be delayed by breastfeeding. Why some patients may experience their first migraine or worsened migraine during pregnancy is unclear, but interrupted sleep, stress, and nausea preventing eating may contribute. Physicians should be careful in these cases to rule out other etiologies which have increased incidence in the puerperium, such as subarachnoid or intracerebral hemorrhage, cerebral venous thrombosis, preeclampsia, and ischemic stroke. Low-pressure headaches from spinal procedures performed during delivery also may occur.

Triggers other than hormonal changes include stress (with some patients having headaches during the "letdown period" after stress, such as on weekends), flickering or bright lights, heat, odors, weather changes, high altitude, medicines (such as Ritalin), and certain foods and drinks. Monosodium glutamate, nitrites (eg, processed meats), and tyramine (aged cheeses, freshly baked breads, pickled/fermented food, liver, yogurt, and figs) often are the culprits. Alcohol, especially if dark-colored, may trigger an attack, with tyramine and flavonoid phenols being implicated. Many individuals with migraine are especially sensitive to chocolate, mainly because of phenylethylamine. Caffeine (more than 300 mg) may cause headaches because of excessive consumption or withdrawal (eg, amount or delay in drinking coffee on weekends). Decreasing caffeine by one cup of coffee or its equivalent per week to two cups or less per day, and even further if insomnia is a problem, can help. Because migraineurs are sensitive to changes, routine schedules, such as sleep patterns and meals, are important. Inconsistent schedules during travel often trigger a migraine.

FAMILIAL MIGRAINES

Many studies have examined the transmission of migraine within families. Russell and Olesen found that first-degree relatives of probands with migraines with aura (MWA) had a 4x increased risk of MWA. Relatives of probands without aura had 1.9x increased risk of migraines without aura (MO). The results suggested that transmission of migraine type within families had some specificity.[3] The mode of inheritance varies; some families show autosomal dominant transmission, while others have autosomal recessive transmission with incomplete penetrance. Monozygotic twins are more concordant for migraine than

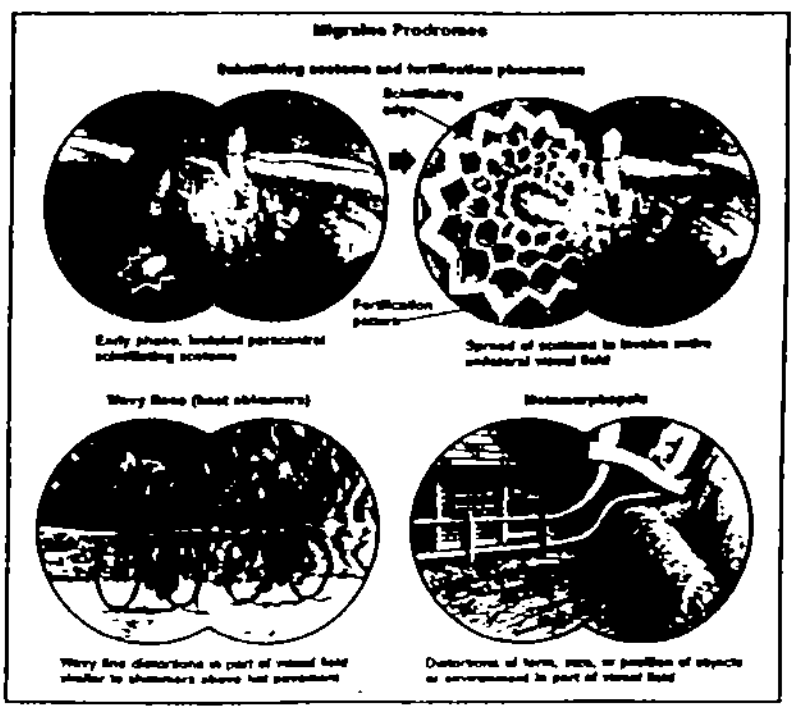

Illustration.—Migraine auras.

dizygotes, further supporting a genetic influence.

Several theories have been offered on the etiology of migraine, with much recent research supporting the trigeminovascular system as the cause or contributing factor. A plexus of largely unmyelinated fibers arising from the trigeminal ganglion surround large cerebral vessels, pial vessels, venous sinuses, and dura mater. The fifth cranial nerve carries sensation from the face and frontal two thirds of the scalp and meninges into the brainstem to the thalamus to the cortex. The trigeminovascular system is activated during migraine, resulting in vasodilation and perivascular neurogenic inflammation.[4] Structural changes also are seen in the dura, such as mast cell degranulation and platelet aggregation in venules. Plasma extravasation can be blocked by ergot alkaloids, indomethacin, acetylsalicylic acid, serotonin ($5HT_{1B/D}$) agonists, such as Imitrex, GABA agonists (ie, Depakote and benzodiazepines), and neurosteroids. Urinary excretion of 5-hydroxyindoleacetic acid, the main metabolite of 5HT, was shown to be increased in migraines. Platelet 5HT has been found to drop during the attacks. Intravenous injection of 5HT stops attacks.[5] Some researchers propose an initial event in the cortex, generating changes in the brainstem and trigeminovascular system. The fact that many patients have prodromes, such as change of appetite or excessive yawning, before migraine supports the researchers' findings.

Several diseases have been found to be associated with migraine, such as stroke, vertigo, epilepsy, psychiatric disorders, as well as other headaches. Recognizing these comorbidities is important for treatment. They may limit therapy, such as using beta blockers, in migraineurs with depression. On the other hand, one medicine might benefit both conditions, such as using Depakote for those also with epilepsy. Comorbidities may exacerbate migraine, and thus need to be treated in order to control headaches.

Strokes especially are increased in MOs and the posterior cerebral artery distribution. In a study of females younger than age 45 with migraine, there was a 3x increased risk of stroke in MO and 6x in MWA. Smoking increased stroke risk to 10x controls (3x greater than females without migraines who smoked). Young women on oral contraceptives (OCP) with migraine showed a risk 14x that of controls without migraines or OCP and 4x the risk of those on OCP without migraines. A dose-effect relationship was shown between the risk of stroke and the dose of estrogen. In none of these cases was the stroke induced by a migraine.[6] Vasoactive therapy for migraine also may be a factor in causing stroke. Migraine and stroke also are associated with the antiphospholipid syndrome.

Car and motion sickness are more common in those with migraines. Slater reported Benign Recurrent Vertigo of Adulthood beginning between ages 7 and 55 and consisting of episodes of vertigo with nausea and vomiting. Incidence increased on awakening and during menses. Duration varied from a few minutes to 4 days. No hearing loss or tinnitus was experienced. The majority had migraines or a strong family history of them.[7]

Ottman and Lipton found a 24% prevalence of migraine in patients with epilepsy.[8] Head injury also is a risk factor for both disorders. Several studies have examined the comorbidity of migraine and psychiatric disorders. Meck et al found an increased rate of depression, bipolar disorder, generalized anxiety disorder, panic disorder, simple phobia, and social phobia in those with migraine.[9]

MIGRAINES AND CHRONIC DAILY HEADACHES

Other types of headaches have been found to be associated with migraine. Sanin categorized 400 patients attending a headache clinic. Tension headache, drug-induced headache, or both were found to be coexisting in 75% of migraine cases. Ninety-six percent of MWA patients also had MO. Of those with chronic daily headache (CDH), 86.9% had migraine as one of their diagnoses.[10]

Mathew et al coined the term "transformed migraine" to describe a common daily or near-daily headache that was seen in 77% of CDH patients at the Houston Headache Clinic.[11] Several factors, including analgesic or ergot overuse, depression, stress, hypertension, and nonheadache medicine (eg, hormones) may contribute to the development of CDH from episodic headache. The transformation is gradual in 80% of patients and sudden in 20%. Trauma to the head or neck, aseptic meningitis, surgery, myelography, and medical illnesses may produce sudden transformation. Medication overuse has been found in 80% of those with CDH and is believed to accelerate pain through a phenomenon called "rebound." Patients are not necessarily abusers of medicine, but merely are trying to remain functional. Some use only one type of medicine, but many take several types. The most common drugs associated with rebound are aspirin, acetaminophen, codeine, and ergotamines. Headaches usually begin 4 to 6 hours after stopping medicine. Most headache specialists recommend limiting pain medicine to 3 days/week or less to avoid development of rebound syndrome.

Migraine treatment entails acute and preventive therapy. Acute treatment involves medicines affecting specific mechanisms causing migraine, analgesics, antiemetics and rehydration, and sedatives to help relax/sleep. For milder headaches, nonsteroidal anti-inflammatory drugs (NSAIDS) may be useful. These especially may be helpful in menstrual migraine but usually need to be started several days before menses. Toradol injections may be needed in more severe cases. Midrin, Ultram, and butalbital compounds also may be beneficial.

The most specific antimigraine agents are serotonin-specific ($5HT_{1D}$) receptor agonists. They cause vasoconstriction, reduce neurogenic inflammation, and may decrease pain transmission in the trigeminal pathway.[12] Available agonists include Imitrex, DHE, and ergotamine. Imitrex is at least as efficacious as ergotamine compounds and oral analgesics. It provides more rapid relief but

has a higher headache recurrence rate.[13] The oral form has a slower onset and less effectiveness than the subcutaneous form. In a study of migraine, subcutaneous Imitrex relieved headache in 78% vs 57% of those treated with DHE injection at 1 hour, 85% vs 73% at 2 hours, and showed similar ratings at 3 hours. Recurrence rate was 45% with Imitrex vs 18% with DHE.[14] The intranasal form of Imitrex is becoming available. A study in which patients used 20 mg in each nostril showed 64% and 75% relief in 1 and 2 hours, respectively, compared to 30% and 32% of patients using a placebo.[15]

Imitrex is generally well tolerated, but a few serious side effects of coronary spasm, myocardial infarction, ventricular arrhythmia, and death have occurred.[15-18] These usually have been in patients with cardiovascular risk factors in whom Imitrex is not indicated. Lewis et al reviewed cardiovascular events associated with Imitrex. That study also showed no myocardial perfusion abnormalities using PET scan after receiving Imitrex in patients at low risk for ischemic heart disease.[19]

Atypical sensations of tingling, tightness, and heaviness in the chest and throat occur more with injections than with pills. There is little clinical evidence that these symptoms are of cardiac origin. EKG monitoring during these complaints has not shown any changes except for in one patient with reversible ST-segment elevation, suggesting vasospasm.[19] Chest tightness is more common in females and usually is associated with breathing difficulties, panic, and paresthesias. It is hypothesized that these "triptan symptoms" common to Imitrex and new $5HT_1$ agonists being investigated may be a result of their affinity for $5HT_{1A}$ receptors involved in the pathogenesis of anxiety.[20] Symptoms also may result from esophageal spasm or bronchoconstriction. Injection site reactions occur in half the patients using the SQ form. It is important to explain these possible side effects to patients. Imitrex is contraindicated in patients with basilar or hemiparetic migraine, prolonged aura, or infarct.

DHE has been shown to be more efficacious than meperidine with hydroxyzine or butorphanol.[21] It has less arterial constriction than ergotamine and Imitrex, but is still contraindicated in those with coronary and peripheral vascular disease. It may be given IV, IM, and SQ. It does not cause sedation but usually requires pretreatment with an antiemetic, which may be sedating. It is especially useful in status migrainosus and transformed migraine. As with ergotamine, it is not advisable to give within 24 hours of using Imitrex.

Intranasal lidocaine has been reported to provide rapid, but short-lasting, relief in some patients.[22] Oral or IV steroids also may be efficacious. Thorazine has been effective in relieving the pain, nausea, and anxiety of migraines. If patients are unresponsive to the above medicines or if they are contraindicated for them, then limited use of narcotics may be necessary. One must be cautious with the possible side effects, addiction, and tolerance. Stadol nasal spray has a rapid onset of pain relief, but a high incidence of nausea, psychological disturbances, and sedation. Because it is an opiate agonist/antagonist, theoretically, it should not cause euphoria and may cause withdrawal for those on other opiates. However, it still has been abused and has led to addiction.[23]

PREVENTION

Preventive medicine is indicated for those who have at least three headaches per month and/or who respond poorly to abortive treatment. It may take several weeks to months for these to produce relief, depending on the dose required. Patients should be warned about this so they will not despair as their dose is being increased without prompt improvement. Daily aspirin or NSAIDS may be helpful in mild cases. Antidepressants, calcium channel blockers, beta blockers, and Depakote have been efficacious. Mathew reported that Neurontin may be useful in treating transformed migraine and is conducting a controlled trial for prophylaxis.[24] Periactin may be helpful primarily in children. As last resorts, monoamine oxidase inhibitors, lithium, or Sansert may be tried, but have more potential serious side effects requiring careful monitoring.

Menstrually related migraine may be treated by one of the above medications on a daily basis or for a few days before and during menses. Sometimes an increased dose of the usual daily medicine perimenstrually will help. Hormonal manipulation also may be helpful, such as taking OCPs the entire month or using percutaneous estradiol just before and during menses. Norplant often worsens migraine, and depo-provera may trigger one. Danazol, tamoxifen, and bromocriptine have been reported to be effective, but have not been studied in clinical trials. Therefore, they are not recommended for common use.[25-27]

PREGNANCY

It is ideal to taper off preventive medicines before planning a pregnancy. If a preventive medicine is necessary, it is best to wait until after the first trimester to begin. Several headache experts recommend propranolol, although it is rated category C for use in pregnancy. Some experts also use amitriptyline, but it is rated category D for use during pregnancy. Tylenol (rated category B) is the safest medicine to use for acute pain. If a stronger medicine is needed, meperidine orally or IM, also rated category B, may be helpful. Although frequently used by obstetricians and neurologists, Tylenol #3 and Darvocet are in category C. A short course of prednisone may be beneficial and is relatively safe. Although there is no evidence that Imitrex is a human teratogen, no well-controlled studies are available evaluating its usage in pregnancy. Therefore, it is not recommended at this time and is listed as category C.

For all of the above medicines, the lowest dose at the longest interval that will help is recommended. Consultation with the patient's obstetrician is recommended, especially because treatments during pregnancy are somewhat controversial. Phenergan or other

antiemetics should be given to treat vomiting and to ensure proper nutrition. Correction of dehydration and electrolyte abnormalities is especially important during pregnancy.

Ideally, patients should avoid medicines while breastfeeding. If required, patients should use shorter-acting forms after a feeding and consider pumping and disposing of the breast milk at the next feeding, depending on the half-life of the drug and interval between feedings.

Nonpharmacologic treatment is important in prophylactic and abortive treatment of migraine, especially during pregnancy. Headache calendars noting times of sleep and meals, foods consumed, and psychological and other stressors may uncover triggers which can be avoided. Aerobic exercise has been shown to decrease the incidence and severity of migraine. Ice, heat, massage, and sleep may help acute pain. Biofeedback and other relaxation techniques (yoga, meditation, relaxing music) may be helpful. Adherence to a migraine diet and to a regular schedule for sleep and meals is advocated. Counseling for problems related to work or family may be required.

CONCLUSION

Migraine is a common cause of disabling headache, especially in women. Overall, women report more severe pain and nausea, more vomiting, more attacks, and more missed work from migraines than do men. Because so many factors affect migraine and should be considered in treatment choice, it is imperative that physicians take the time to get to know the whole patient. Patients need to be educated about their diagnosis and be reassured that effective treatment is available.

REFERENCES

1. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. *JAMA* 1992;267:64-69.
2. Whitty CWM, Hockaday JM, Whitty MM. The effect of oral contraceptives on migraine. *Lancet* 1966;1:856-896.
3. Russell MB, Olesen J. Increased familial risk and evidence of genetic factor in migraine. *BMJ* 1995;311: 541-544.
4. Feniuk W, Humphrey PPA, Perren MJ. Rationale for the use of 5-HT_1-like agonists in the treatment of migraine. *J Neurolo* 1991;238: 557-561.
5. Hillis WS, MacIntyre PD. Sumatriptan and chest pain. *Lancet* 1993;341: 1564-1565.
6. Tzourio C, Tehindrazanarivelo A, Iglesias S, et al. Case-control study of migraine and risk of ischaemic stroke in young women. *BMJ* 1995;310: 830-833.
7. Slater R. Benign recurrent vertigo. *J Neurol Neurosurg Psychiatry* 1979; 42:363-367.
8. Ottman R, Lipton RB. Comorbidity of migraine and epilepsy. *Neurol* 1994;44:2105-2110.
9. Merikangas KR, Angst J, Isler H. Migraine and psychopathology. Results of the Zurich cohort study of young adults. *Arch Gen Psych* 1990;47: 849-853.
10. Sanin LC, Mathew NT, Bellmeyer LR, Ali S. The International Headache Society (IHS) Headache Classification as applied to a headache clinic population. *Cephalgia* 1994;14:443-446.
11. Mathew NT, Reuveniu, Perez F. Transformed or evolutive migraine. *Headache* 1987;27:102-106.
12. Moskowitz MA. Neurogenic inflammation in the pathophysiology and treatment of migraine. *Neurol* 1993;43:16-20.
13. Bateman DN. Sumatriptan. *Lancet* 1993;341:221-224.
14. Winner P, Ricalde O, Le Force B, et al. A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. *Arch Neurol* 1996; 53:180-184.
15. Plosker GL, McTavish D. Sumatriptan: reappraisal of its pharmacology and therapeutic efficacy in the acute treatment of migraine and cluster headache. *Drugs* 1994;47:622-651.
16. Castle WM, Simmons VE. Coronary vasospasm and sumatriptan. *BMJ* 1992;305:117-118.
17. Chester AH, O'Neil GS, Yacoub MH. Sumatriptan and ischaemic heart disease. *Lancet* 1993; 341:1419-1420.
18. Mueller L, Gallagher RM, Ciervo CA. Vasospasm-induced myocardial infarction with sumatriptan. *Headache* 1996;36:329-331.
19. Lewis PJ, Barrington SF, Marsden PK, Marsey MN, Lewis LD. A study of the effects of sumatriptan on myocardial perfusion in healthy female migraineurs using $^{13}NH_3$ positron emission tomography. *Neurol* 1997;48: 1542-1550.
20. Lai M, Loi V, Cherchi A, Pisano R, Del Zompo M. Can sumatriptan be anxiogenic in migraineurs? *Cephalgia* 1996;16:384-385.
21. Belgrade MJ, Ling LJ, Schleevogt MB, Ettinger MG, Rulz E. Comparison of single-dose meperidine, butorphanol, and dihydroergotamine in the treatment of vascular headache. *Neurol* 1989;39:590-592.
22. Maizels M, Scott B, Cohen W, et al. Intranasal lidocaine for treatment of migraine. *JAMA* 1996;276: 319-321.
23. Fisher M, Glass S. Butorphanol (Stadol): a study in problems of current drug information and control. *Neurol* 1997;48:1156-1160.
24. Mathew N. Gabapentin in migraine prophylaxis. *Cephalgia* 1996;16:367.
25. Sarno AP. Premenstrual syndrome: beneficial effects of periodic, low-dose danazol. *Obstet Gynecol* 1987;70: 33-36.
26. Powles TJ. Prevention of migrainous headaches by tamoxifen. *Lancet* 1986;2:1344.
27. Anderson AN, Larsen JF, Steenstrup OR, Svendstrup B, Nielsen J. Effect of bromocriptine on the premenstrual syndrome. A double-blind clinical trial. *Br J Obstet Gynecol* 1977;84: 370-374.