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Primary Care Reports™

The Practical, Peer-Reviewed Journal for Primary Care and Family Physicians

Volume 15, Number 11 **November 2009**

Headaches are one of the most common problems of patients presenting to primary care physicians. Workup and management can be both frustrating and demanding. The physician always needs to be wary of serious conditions such as brain tumors and giant cell arteritis, which would be disastrous to miss but are rather uncommon.

—The Editor

Common Headache Disorders: Diagnosis and Management, Part I

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Headache is the seventh most common presenting complaint for outpatient physician visits in the United States. The problem of headache generates 18.3 million ambulatory encounters in the United States per year.[1]

Headaches generally are differentiated into primary (idiopathic) headache syndromes (*see Table 1*), which include migraine, tension-type, and cluster headache, and secondary headaches caused by underlying disease. This review will focus on the common primary headache syndromes.

Migraine is a syndrome of intermittent, moderate- to severe-intensity headaches lasting from four to 72 hours.[2] The headaches typically are unilateral, throbbing in quality, and associated with nausea or vomiting, and sensitivity to light and/or noise. Aura, usually visual with scintillating scotomata or fortification spectra, precedes the headache in about 15-20% of people.

Tension-type headache typically is described as a band-like pressure headache without associated symptoms. The International Headache Society (IHS)[2] defines tension-type headache as a bilateral headache having a pressing or tightening quality of mild to moderate severity. Unlike migraine, it is not aggravated by physical activity, nor is it associated with vomiting. By definition, chronic tension-type headache occurs at least 15 days per month for at least 6 months, [2] although in clinical practice, it usually is a daily or almost daily headache.

The clinical presentation of cluster headache is a unilateral headache of excruciating severity, accompanied by certain autonomic phenomena that is more common in men and strikingly periodic in occurrence.[2] Cluster headache is marked by cycles of headache lasting one to four months, separated by remissions of

Statement of Financial Disclosure

To reveal any potential bias in this publication, we disclose that Dr. Greg Wise, Editor-in-Chief, serves on the speaker's bureau for The Medicine Company. Dr. Jamieson (peer reviewer) reports that she is a retained consultant for Boehringer Ingelheim, Merck, and Ortho-McNeil and serves on the speaker's bureau for Boehringer Ingelheim and Merck. Dr. Solomon (author), Mr. Underwood (Associate Publisher), and Ms. Mark (Specialty Editor) report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

six to 24 months. The cluster headache attacks are unilateral and located around the eye, temple, or upper jaw. Associated symptoms may include conjunctival reddening and tearing of the eye, drooping of the eyelid, nasal stuffiness, and rhinorrhea. The attacks generally last from 15 minutes to three hours (average 45 minutes), occur every other day to eight times daily, and often awaken the patient after 90 to 120 minutes of sleep. Ten to 15% of cluster patients suffer with chronic cluster headache that lasts more than one year without remission.

Prevalence of Headache

In order to determine the overall prevalence of headache in the general population, Rasmussen and colleagues[3] examined 740 persons randomly chosen to constitute a representative sample of the population of Copenhagen, Denmark. The group was aged 25-64 years old and was representative of the Danish population in terms of sex, age distribution, and marital status. Subjects underwent a structured interview, examination by a neurologist, and laboratory evaluation. Headache disorders were classified according to the International Headache Society (IHS) criteria.[2] They reported a lifetime prevalence of headache of 96%, which was significantly higher among women (99%) than among men (93%). Men aged 55-64 had the lowest lifetime and last year prevalence of headache. Headache at the time of examination (point prevalence rate) was twice as common in women as in men.

The overall lifetime prevalence of migraine was 16% (25% among women and 8% among men). The male/female ratio was about 1:3. There were no significant differences in migraine prevalence rates according to age. Of migraine sufferers, 15% had migraine 8-14 days per year, and 9% had it more than 14 days per year. Eighty-five percent of migraineurs reported severe pain intensity.

The lifetime prevalence of tension-type headache was 78% (88% among women and 69% among men). The male/female ratio was about 4:5. Men aged 55-64 had the lowest lifetime prevalence of tension-type headache. Among women, there was a significant decrease in prevalence of tension-type headache with increasing age. Of tension-type headache sufferers, 23% had headache 8-14 days per year, and 36% had it several times per month. Chronic tension-type headache (tension-type headache occurring ≥ 180 days/year) was noted by 3% of the population. Only 1% of tension-type headache patients reported severe pain intensity, while moderate pain was noted by 58%, and mild pain by 41%.

To determine trends in the prevalence of chronic migraine and the impact on disability and utilization of medical care, the National Health Interview Survey[4] (NHIS) collected data through personal interviews conducted with a representative sample of the U.S. population to determine the prevalence of migraine. This study compared migraine prevalence for 1980 and 1989. The NHIS study showed that more than 80% of female and 70% of male migraine sufferers had at least one physician contact per year because of migraine headaches. Eight percent of female and 7% of male migraine patients were hospitalized at least once per year for migraine. Long-term limitations in functional capacity due to migraines were reported by 3% of females and 4% of males.

"Chronic daily headache," a term not included in the ICHD classification, encompasses a group of headache disorders lasting longer than 6 months and marked by a duration of four hours or more for at least half of the days of the month.[5] The most common daily headache syndromes include chronic tension-type headache with or without medication overuse, chronic migraine, or medication overuse headache in patients with frequent migraine attacks. Factors associated with the development of chronic daily headache were higher baseline headache frequency, obesity, arthritis, diabetes, and snoring.[6]

Population-based studies in the United States, Europe, and Asia report that approximately 4% of the general population suf-

Executive Summary

- Lifetime prevalence of headaches reaches 98% in women. The lifetime prevalence of migraine is 25% in women and can occur with and without auras.
- The International Classification of Headache Disorders provides a systematic approach to the diagnosis and nomenclature of headaches.
- Migraine headaches have distinct diagnostic patterns and often respond effectively to specific prophylactic and therapeutic options.

Primary Care Reports™, ISSN 1040-2497, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

ASSOCIATE PUBLISHER: Russ Underwood.
SPECIALTY EDITOR: Shelly Morrow Mark.
DIRECTOR OF MARKETING: Schandale Kornegay.
GST Registration Number: R128870672.

POSTMASTER: Send address changes to ***Primary Care Reports***™, P.O. Box 740059, Atlanta, GA 30374.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

Back issues: $26. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.

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Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $369
Add $17.95 for shipping & handling
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Table 1. The International Classification of Headache Disorders[2]

1. MIGRAINE

1.1 Migraine without aura

A. 5 or more attacks

B. Headaches last 4-72 hours (untreated or unsuccessfully treated)

C. Headache has at least 2 of the following characteristics:

1. unilateral
2. pulsating
3. moderate or severe pain
4. aggravated by routine physical activity

D. During headache at least 1 of the following:

1. nausea and/or vomiting
2. photophobia and phonophobia

E. Not caused by another disorder

1.2 Migraine with aura

A. At least 2 attacks fulfilling criterion B

B. Aura consisting of at least 1 of the following, but no motor weakness:

1. fully reversible visual symptoms including positive features (eg, flickering lights, spots or lines) and/or negative features (ie, loss of vision)
2. fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
3. fully reversible dysphasic speech disturbance

C. At least two of the following:

1. homonymous visual symptoms and/or unilateral sensory symptoms
2. symptoms develop gradually over 5 minutes
3. symptoms last between 5 and 60 minutes

E. Not caused by another disorder

2. TENSION-TYPE HEADACHE (TTH)

2.1 Episodic tension-type headache

A. Headache lasting from 30 minutes to 7 days

B. Headache has at least 2 of the following characteristics:

1. bilateral location
2. pressing/tightening (non-pulsating) quality
3. mild or moderate intensity
4. not aggravated by routine physical activity

C. Both of the following:

1. no nausea or vomiting (anorexia may occur)
2. no more than one of photophobia or phonophobia

D. Not caused by another disorder

2.3 Chronic tension-type headache

Same as episodic tension-type headache except

A. Headache occurs on >15 days/month on average for > 3 months (>180 days/year) and fulfilling criteria B-D

B. Headache may last hours or may be continuous

D. Both of the following:

1. no more than one of photophobia, phonophobia or mild nausea
2. neither moderate or severe nausea nor vomiting

3.1CLUSTER HEADACHE

A. 5 or more attacks

B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes if untreated

C. Headache is accompanied by at least 1 of the following:

1. ipsilateral conjunctival injection and/or lacrimation
2. ipsilateral nasal congestion and/or rhinorrhea
3. ipsilateral eyelid swelling
4. ipsilateral forehead and facial sweating
5. ipsilateral miosis and/or ptosis
6. a sense of restlessness or agitation

D. Attacks have a frequency from 1 every other day to 8/day

E. Not caused by another disorder

8.2 MEDICATION-OVERUSE HEADACHE

A. Headache present on ≥ 15 days/month

B. Regular overuse for > 3 months of one or more drugs that can be taken for symptomatic treatment of headache

C. Headache has developed or markedly worsened during medication overuse

D. Headache resolves or reverts to its previous pattern within 2 months after discontinuation of overused medication

Adapted from reference 2.

fers from chronic daily headache.[7,8,9,10,11,12] In addition, 0.5% of the population has severe headache on a daily basis.[13]

Population-based studies report that the most common cause of chronic daily headache is chronic tension-type headache (1.4-2.7%), followed by chronic migraine (1.0-1.7%).[14] In tertiary headache centers, the most common cause of chronic daily headache is chronic migraine. Studies report that chronic daily headache is roughly twice as prevalent in women as in men.[14] The average age at onset of chronic daily headache is in the thirties. The prevalence of chronic daily headache appears consistent across age groups from childhood and adolescence, adults, and the elderly.[14] This is in contrast to migraine, which decreases in prevalence after the sixth decade of life.

Evaluation of the Headache Patient

Headache is one of the most common pain complaints of humankind. Headache may be categorized simply as a primary headache disorder or secondary (organic) headache. Secondary

Table 2. Data Necessary to Establish Thorough Patient History[25]

- Age of onset/precipitating events
- Description of headache
  - Temporal pattern
  - Prodromal or aura symptoms
  - Location
  - Frequency
  - Severity
  - Duration
  - Associated symptoms
  - Does pain change with exertion or position?
  - Aggravating or alleviating factors
- Use of headache medications — response to past treatment
- Use of other medications/ comorbid conditions
- Allergies/sensitivities
- Sleep pattern
- Family history
- Medical, surgical, OB history
- Previous testing and results
- Psychosocial history
- Use of tobacco, alcohol, caffeine

headaches present as a symptom of an underlying disease (i.e., giant cell arteritis, meningitis), while benign headaches are classified further based on clinical symptomatology, i.e., temporal patterns and accompanying symptoms, into syndromes such as migraine, tension-type headache, and cluster headache.

The Headache History

The headache history is the key to determining whether a headache is migraine, cluster, tension-type, or whether it represents a symptom of underlying disease. Most often a careful and complete history will provide a presumptive diagnosis, which then can be verified by physical examination and, when necessary, confirmatory laboratory or radiographic studies.[15]

Evaluating factors such as age of onset, temporal pattern, quality and location of pain, and trigger factors usually allows the physician to diagnose the headache problem and initiate therapy. (*See Table 2.*)

Duration. The duration of the headache problem often is a key indicator to probable underlying cause. Severe headache of sudden onset, especially if associated with focal neurological signs or changes in level of consciousness, suggests serious illness such as subarachnoid hemorrhage (SAH) or meningitis. Recurrent intermittent headaches occurring for many years more likely represent migraine headaches. A long history of daily headaches without associated symptoms is suggestive of chronic tension-type headache.

The patient's initial migraine headache, unless preceded by a characteristic aura, may be confused with serious neurological problems such as meningitis or subarachnoid hemorrhage.

Among the most difficult headaches to interpret are those developing over weeks or months. These may be benign or may arise from conditions as diverse as sinusitis, ocular disease, subdural hematoma, mass lesion, or — in the patient older than 60 years — giant cell arteritis.

Timing. After establishing the frequency and duration of the headache, the timing with respect to other physiological events can be helpful in the diagnosis of recurrent headache. One should inquire as to the time of day the headache occurs and its relationship to puberty, menses, pregnancy, menopause, or the use of hormones.

The initial onset of migraine in women often is during puberty. Migraine may resolve following menopause. It may occur irregularly for months to years or it may follow a regular pattern of occurring with menses. An acute migraine attack can last from four to 72 hours, with headache-free intervals between attacks.

Episodic cluster headache follows a pattern of cyclic bouts of attacks lasting from two weeks to several months. These bouts are separated by headache-free periods lasting from months to years. During a cluster cycle, severe headaches lasting from 15 minutes to three hours may occur from one to four times a day, often awakening the patient from sleep at night.

The duration of the cluster headache attack distinguishes it from trigeminal neuralgia, which presents with recurrent jabs of pain lasting less than a minute. Trigeminal Autonomic Cephalgias or TACs (*see Table 3*), such as chronic paroxysmal hemicrania, show a pain pattern similar to cluster headache, but attacks are more frequent and predominantly occur during the day.[2,16]

Chronic tension-type headaches show no periodicity and have few prolonged headache-free intervals. The patient typically describes a daily or almost daily headache.

Location. Location of the head pain can aid in the diagnosis of cluster headache or trigeminal neuralgia, but it is less specific in migraine and tension-type headache. Although migraine is unilateral two-thirds of the time, it is bilateral one-third of the time. Chronic tension-type headache usually is bilateral but may be unilateral. Cluster headache and trigeminal neuralgia are almost always unilateral. Migraine usually alternates sides with different attacks but may be predominantly unilateral throughout life. Cluster headache is invariably unilateral and affects only one side during a series of attacks. Trigeminal neuralgia usually occurs in the V2 or V3 distribution, while TACs usually occur in the V1 distribution.[17]

Quality. Migraine usually is throbbing or pulsatile, whereas a constant pressure suggests tension-type headache, and deep, boring, intense pain points to cluster headache. Trigeminal neuralgia is marked by short, intense, shock-like jabs.

The intensity of pain in cluster headache and trigeminal neuralgia is invariably described as excruciating so that the cluster headache patient usually cannot remain still. The migraine sufferer, by contrast, often chooses to rest in a dark, quiet room.

Associated Symptoms. If the patient tells of an aura or warning signs, this generally means migraine with aura (classic migraine). Visual or neurological symptoms commonly precede the headache by four to 60 minutes (typically 20 minutes). Premonitory symp-

Table 3. Trigeminal Autonomic Cephalalgias (TACs)[2,16]

	CPH	EPH	SUNCT	CLUSTER
Sex F:M	3:1	1:1	1:2.3	1:4
Attacks/day	1-40	3-30	3-200	0-8
Attack duration	2-45 min	1-30 min	5-240 s	15-180 min
Indomethacin response	++	++	No	+/-

CPH: chronic paroxysmal hemicrania
EP: episodic paroxysmal hemicrania
SUNCT: short duration unilateral neuralgiaform headache with conjunctival injection and tearing

Hemicrania Continua (HC): Side-locked unilateral headache, daily and continuous, moderate intensity with exacerbations of severe pain. Ipsilateral autonomic symptoms (conjunctival injection and/or tearing, nasal congestion and/or rhinorrhea, ptosis and/or miosis) during exacerbations. Complete response to indomethacin.

toms, which can include euphoria, fatigue, yawning, or craving for sweets, may occur 12-24 hours before an attack.

Associated symptoms that may accompany migraine include photophobia, phonophobia, osmophobia, anorexia, nausea, vomiting, and focal neurological signs. Symptoms seen with cluster headache and other TACs include partial Horner's syndrome, constricted pupils, injected conjunctiva, and unilateral lacrimation and rhinorrhea.

Neck stiffness or other signs of meningeal irritation can signal meningitis or subarachnoid hemorrhage. A mass lesion, hydrocephalus, or encephalitis may be suggested by decreased level of consciousness or obtundation. Seizures can reflect cortical irritation resulting from a mass lesion, such as a tumor or arteriovenous malformation. Fever and sweating may suggest an infectious process.

Precipitating Factors. Fatigue, particularly loss of sleep, may trigger either migraine or tension-type headache. Stress may exacerbate tension-type headache, whereas migraine may occur after stressful events, often on weekends or vacations. Migraine sufferers may associate their headaches with menses, missing meals, or consuming foods such as red wine, chocolate, or aged cheese. Alcohol may trigger a cluster attack during a series but will have no effect during a quiescent period. Weather changes can be associated with migraine. Commonly associated with chronic tension-type headache are symptoms of depression, such as sleep and appetite disturbances.

One also should assess possible exposure to occupational toxins, chemicals, or infectious agents. Carbon monoxide poisoning, for example, often manifests as headache. Certain chemicals such as nitrates induce withdrawal and reintroduction headache. Exposure to infectious agents in immunosuppressed or AIDS patients may induce meningitis unaccompanied by classic fever and stiff neck.

Past History. Migraine is a familial disorder, with a positive family history in two-thirds of cases. Cluster headache is familial in only about 3% of patients.[18] In tension-type headache, a family history of depression or alcohol abuse is common.

The patient's medical-surgical history and history of current and previous medications can aid in diagnosis. Head trauma, for instance, may suggest subdural hematoma or skull fracture. Certain medications can trigger the onset of headache or exacerbate headache in patients with an underlying headache disorder.[19,20] Medication-induced headache has been reported commonly with the following medications: indomethacin (Indocin), nifedipine (Procardia, Adalat), cimetidine (Tagamet), atenolol (Tenormin), trimethoprim-sulfamethoxazole (Bactrim, Septra), nitroglycerin, isosorbide dinitrate (Isordil), ranitidine (Zantac), isotretinoin (Retin-A), captopril (Capoten), piroxicam (Feldene), granisetron (Kytril), erythropoetin (Epogen), metoprolol (Lopressor, Toprol), and diclofenac (Voltaren). Medications that may aggravate existing migraine include vitamin A, its retinoic acid derivatives, and hormonal therapy, such as oral contraceptives, clomiphene, and postmenopausal estrogens. Migraine and cluster headaches may be exacerbated by vasodilators such as nitrates, hydralazine (Apresoline), minoxidil (Loniten), nifedipine (Procardia, Adalat), and prazocin (Minipress).

Reserpine can cause depression, migraine, and tension-type headaches. Indomethacin, while useful in treating some TACs such as paroxysmal hemicrania or hemicrania continua, can cause a generalized headache. Frequent or chronic use of some prescription and over-the-counter medications used to treat headache, including opioids, barbiturates, caffeine, triptans, and ergots, can lead to medication overuse (rebound) or withdrawal headaches.[21]

Physical Examination

After evaluating the headache history, the physician should perform a targeted physical examination. This should include a mental status exam (often performed as part of obtaining the history), blood pressure and pulse measurement, examination of the cranial nerves, fundoscopic exam, palpation of the head and neck, evaluation of motor and balance, and palpation of peripheral pulses (particularly if vasoconstrictor medications are to be prescribed). (*See Table 4.*)

Diagnostic Testing

Diagnostic testing of the headache patient should be based on the results of the history and physical examination. In a patient with a typical headache history of several years' duration and a normal neurological examination, no further evaluation is usually needed. All patients older than 60 with new-onset headache or change in their headache pattern should have a sedimentation

Table 4. Key Aspects of Physical Examination[25]

- Observation and palpation of head for signs of trauma, tenderness, adequacy of temporal artery pulses
- Assessment of cranial nerves including fundoscopic evaluation
- Examination of oral cavity
- Assessment of temporomandibular joints for alignment, ease of mobility, and "clicking"
- Palpation of neck for lymphadenopathy and thyromegaly; auscultation over carotids
- Assessment of cervical motion for meningeal irritation or spinal abnormalities
- Palpation of areas including suboccipital and supraorbital notches for tenderness
- Assessment of muscle strength in upper and lower extremities
- Assessment of tactile sense
- Testing of deep-tendon reflexes
- Examination of ears, throat, lungs, heart, and abdomen for systemic disease
- Screening for postural abnormalities, skeletal asymmetry, scoliosis, spasm, additional trigger points in neck, shoulders, and back

Table 5. Red Flags in the Diagnosis of Headache[25]

- Onset of headache after age 50
- Onset of new or different headache
- "Worst" headache ever experienced
- Onset of subacute headache that progressively worsens over time
- Onset of headache with exertion, sexual activity, coughing, or sneezing
- Headache associated with any of the following changes in neurological evaluation:
  - Drowsiness, confusion, memory impairment
  - Weakness, ataxia, loss of coordination
  - Numbness and/or tingling in extremities
  - Paralysis
  - Sensory loss associated with headache
  - Asymmetry of pupillary response, deep tendon reflexes, or Babinski response
  - Signs of meningeal irritation
  - Progressive visual or neurological changes
  - Other evidence to suggest an underlying neurological disorder, such as persistent tinnitus, loss of sense of smell, loss of sensation over the face, dysphagia, etc.
- Abnormal medical evaluation:
  - Fever
  - Stiff neck
  - Hypertension
  - Weight loss
  - Tender, non-pulsatile temporal arteries
  - Papilledema
  - Evidence to suggest a systemic illness

rate or C-reactive protein measurement to evaluate for giant cell arteritis. If elevated, a temporal artery biopsy may be obtained to confirm the diagnosis.

Laboratory screening with complete blood count, urinalysis, and chemistry profile adds little diagnostic information. These studies may help to rule out diseases that present with headache if the history and/or examination suggest secondary headache.

Several commonly ordered tests have little or no value in the headache evaluation.[22] Electroencephalography (EEG) may be abnormal in some migraine patients, but EEG changes are neither specific for nor diagnostic of migraine. As a screening test to localize organic lesions, EEG has been supplanted by more specific CT and MR imaging. Evoked potentials (visual, auditory, and somatosensory) fail to show specific findings in migraine. Like EEG, evoked potentials have no utility as a screening test for headache. Cervical spine X-rays rarely are useful in the diagnosis and management of headache patients.

Neuroradiology has little role in the diagnosis of headache beyond ruling out occult lesions such as neoplasm, hemorrhage, vascular malformations, brain abscesses, hydrocephalus, or congenital malformations (i.e., Arnold-Chiari malformations). MRI and CT will not pick up other organic etiologies of headache, such as idiopathic intracranial hypertension (pseudotumor cerebri), glaucoma or eye disease, and metabolic or toxic causes of headache. It is critical that the physician obtain a complete history and examination and not rely solely on the MRI or CT to eliminate organic causes of headache.

Most patients suffering with newly developed, acute onset, severe headaches should undergo imaging with CT or MRI to rule out the organic causes listed above. (*See Table 6.*) Because organic causes of headache are rare (estimated at less than 1% in headache clinics), these tests generally will be unrevealing. The benefits of a normal CT or MRI in reassuring the patient and doctor should be considered, however. Some patients (and physicians) may be unwilling to embark on a course of therapy for a benign headache disorder without the reassurance of a normal scan.

A controversy in headache management is the issue of repeated evaluations to look for organic etiologies of headache. Most physicians agree that repeating the pertinent headache history and the targeted physical examination is important to pick up clues for new diagnoses and diagnoses missed at initial evaluation. The issue of obtaining additional CT or MRI scans is unsettled. It generally is prudent to repeat neuroradiographic imaging in a patient whose condition is deteriorating, or where history or physical examination has revealed new neurological abnormalities. There appears to be little yield to obtaining repeated studies in patients whose headache course is stable, even if the patient is not responding well to treatment.

In summary, the appropriate screening for the outpatient with recurrent headaches includes: a complete headache history; both physical and neurologic examination; lab tests only if indicated

Table 6. Guidelines for Use of CT and MRI[25]

The use of neuroimaging procedures may be indicated when *any* of the following is present:

- Drowsiness, confusion, memory impairment
- Onset of pain with exertion, sexual activity, coughing, or sneezing
- Headache that progressively worsens over time
- Signs of meningeal irritation
- Focal neurological signs
- Onset of headache after age 50
- "Worst" headache ever experienced
- Headache not fitting a defined pattern

The use of neuroimaging procedures may *not* be indicated when *all* of the following are present:

- History of similar headaches
- Normal vital signs
- Alertness and cognition intact
- Supple neck
- No focal neurological signs
- Improvement in headache without medications

from history and physical; CT or MRI, if the headaches are of recent onset, if indicated by troubling neurologic symptoms in the history, or if associated with abnormalities on the neurologic examination.

Differential Considerations

In primary care, most headaches are not caused by underlying disease. It is important to recognize, however, that headache can be the presenting symptom of several diseases. Fever, regardless of etiology, is probably the most common medical problem that causes headache. Less common causes include pheochromocytoma, chronic renal failure, hyperthyroidism, and malignant hypertension.[21] Rheumatologic diseases may have headache as an early manifestation. Headache is common in systemic lupus erythematosus, polyarteritis nodosa, and giant cell arteritis. About two-thirds of patients with fibromyalgia report headache, usually tension-type headache. Many types of vasculitis can also present with headache.[21] Headache upon awakening may be the initial symptom of sleep apnea syndrome. The headache often will improve as the day progresses. Associated symptoms include snoring, daytime somnolence, hypertension, and arrhythmias.[21]

Once a primary (benign) headache diagnosis is made, the major role of the physician is to initiate a therapeutic plan. Important goals of the therapeutic plan are to limit disability caused by headache and to prevent the development of analgesic overuse headache.

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Physician CME Questions

22. Common food triggers for migraine include all *except*:
    A. nitrates/nitrites
    B. buckwheat
    C. chocolate
    D. red wine

23. The primary headache more common in men than women is:
    A. migraine
    B. chronic tension-type
    C. cluster
    D. medication overuse headache

24. Evaluation of a patient age 70 with a new-onset headache should include:
    A. sed rate or C reactive protein
    B. EEG
    C. auditory evoked response
    D. all of the above

25. Which of the following headaches is most commonly unilateral in presentation?
    A. cluster headache
    B. subarachnoid hemorrhage
    C. migraine
    D. tension headache

CME Answer Key

22. B; 23. C; 24. A; 25. A

Primary Care Reports

CME Objectives

Upon completion of this educational activity, participants should be able to:

• summarize recent, significant studies related to the practice of primary care medicine;

• evaluate the credibility of published data and recommendations related to primary care medicine;

• discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

United States Postal Service
Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
Primary Care Reports	1 0 4 0 - 2 4 9 7	10/01/09
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$369.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta,
Fulton County, GA 30305
Contact Person: Robin Salet
Telephone: 404/262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*
AHC Media LLC, 525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*
Publisher *(Name and Complete Mailing Address)*
Robert Mate, President and CEO
AHC Media LLC, 525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305
Editor *(Name and Complete Mailing Address)*
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10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
AHC Media LLC	3525 Piedmont Road, Bldg. 6, Ste 400
	Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Thompson Publishing Group Inc.	805 15th Street, NW, 3rd Floor
	Washington, D.C. 20005

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The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
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13. Publication Name: Primary Care Reports
14. Issue Date for Circulation Data Below: September 2009

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Iss Published Nearest to Filing Dat
a. Total No. Copies *(Net Press Run)*			552	493
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	358	353
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	9	8
	(4)	Other Classes Mailed Through the USPS	46	40
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			413	401
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	17	17
	(2)	In-County as Stated on Form 3541	0	0
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f. Total Free Distribution *(Sum of 15d and 15e)*			37	37
g. Total Distribution *(Sum of 15c and 15f)*			450	438
h. Copies Not Distributed			102	55
i. Total *(Sum of 15g, and h.*			552	493
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			92%	92%

16. Publication of Statement of Ownership
Publication required. Will be printed in the November 2009 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: President and CEO — Date: 9/27/09

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Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 14, NUMBER 11 PAGES 21-22 NOVEMBER 2009

Dabigatran vs warfarin: Less bleeding?

Source: Connolly SJ, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-1151.

Numerous prospective trials have confirmed that anticoagulant therapy with warfarin (WRF) provides substantial stroke risk reduction for patients with atrial fibrillation (AF). Overall, AF patients enjoy as much as a two-thirds reduction in risk of ischemic stroke when WRF has been compared with placebo in clinical trials. These benefits notwithstanding, utilization of WRF is complex and entails significant risk of bleeding. Direct thrombin inhibitors (DTIs) such as ximelagatran have previously demonstrated comparable stroke risk reduction in AF as WRF, with less risk of serious bleeding; additionally, direct thrombin inhibitors do not require ongoing monitoring to assure a therapeutic range, simplifying the level of involvement required of the patient. Unfortunately, clinical trials with earlier DTIs (e.g., ximelagatran) showed a significant risk of hepatotoxicity, precluding clinical use in the United States.

Dabigatran (DAB) is an oral DTI administered twice daily. Based upon favorable results from pilot trial data in AF and venous thromboembolism, a major clinical trial (n = 18,113) was undertaken to compare warfarin with DAB in AF.

After a median follow-up of 2 years, DAB fulfilled expectations that it provided risk reduction as great as or superior to WRF, with similar or fewer bleeding events. The orally administered DTI class shows great promise as an alternative to WRF. ■

Does SHBG increase risk of diabetes?

Source: Ding EL, et al. Sex hormone-binding globulin and risk of type 2 diabetes in women and men. *N Engl J Med* 2009;361:1152-1163.

Sex hormone-binding globulin (SHBG) is a protein that might seem to be most interesting to the endocrinologist, since its sole function — until very recently — has been thought to be regulation of the availability of gonadal steroids. For instance, in women with acne, the primary therapeutic effect of estrogen therapy (as in oral contraceptives) is that estrogen increases SHBG levels; the increased SHBG binds plasma testosterone, leaving less free (unbound) testosterone to drive acne.

It may be that SHBG has other pertinent functions. The Women's Health Study provided the data set from which the relationship between plasma SHBG and incidence of type 2 diabetes could be examined. Comparing the SHBG level in women with newly diagnosed diabetes to controls (total n = 718), a steep inverse linear relationship between SHBG and odds ratio for developing type 2 diabetes was demonstrated. Compared to women in the lowest quartile of SHBG, those in the highest quartile were more than 10 times less likely to have incident diabetes. Corroborating results were found in men looking at a similar population from the Physician's Health Study. The mechanism by which SHBG affects diabetes risk is speculated to be related to direct modulation of gonadal steroids on tissues, but is otherwise ill-defined.

There are identified genes associated with production of SHBG. Both SHBG levels and gene identification may become useful to predict risk of type 2 diabetes. ■

Effect of CYP2C19 variants on clopidogrel

Source: Shuldiner AR, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA* 2009;302:849-857.

Clopidogrel (CPG) and aspirin (ASA) are widely utilized as antiplatelet agents for both primary and secondary prevention of cardiovascular disease. Because platelet activation, adhesion, and aggregation are modulated by multiple redundant pathways, it should come as no surprise that any single pharmacologic intervention might be imperfect in its ability to curtail platelet activity. Additionally, even when an antiplatelet agent is mechanistically highly effective, intra-individual variations in metabolism and genetics exert great influence on pharmacokinetics.

CPG must be converted into an active metabolite by the P450 2C19 pathway to functionally impair platelet activity. The impact of genetic variations in 2C19 activity may be examined in vitro through platelet aggregometry. If the laboratory discerns meaningful differences in platelet activity related to genetic variations in 2C19, the next question would be whether such factors impact clinical endpoints.

Chromosomal analysis indicates a strong relationship between genetic variations in 2C19 activity and platelet aggrega-

bility in response to clopidogrel, consistently predicting incomplete CPG activity upon platelets.

After confirmation of the 2C19-clopidogrel relationship, a population of individuals undergoing PCI (after which clopidogrel treatment is standard) were followed for 1 year. During this year, those with genetic variants impairing the antiplatelet activity of CPG were more than twice as likely to incur a CV ischemic event or death. In the future, therapeutic choices may be directed by knowledge of such genetic variation. ■

Denosumab for osteoporosis

Source: Cummings SR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361:756-765.

It appears that osteoporosis (OSPS) is the end result of a war lost by the osteoblasts to the conquering osteoclasts, whether by frailty of the former, vociferousness of the latter, or some similar combination of factors. Indeed, our most popular tools for the prevention and treatment of OSPS — bisphosphonates — mediate improvements in bone mineral density through downregulation of osteoclasts.

Denosumab is an antibody against the activator of osteoclasts called RANKL. Once RANKL is antibody-blocked, osteoclast activity is reversibly inhibited. Denosumab has the desirable characteristic of only requiring a subcutaneous injection every 6 months.

The study by Cummings et al enrolled almost 8000 osteoporotic women who were randomized to denosumab or placebo twice yearly for 3 years. Over that interval, a 40%-60% decrease in hip fracture and vertebral fracture was seen (compared to placebo), with no incidence of the osteonecrosis that has been troublingly reported (albeit rarely) with bisphosphonates. The favorable tolerability of this agent (adverse effect profile similar to placebo) adds to the allure of this yet-to-be approved alternative for OSPS. ■

CRP and HTN treatment

Source: Fulop T, et al. C-reactive protein among community-dwelling hypertensives on a single-agent antihypertensive treatment. *J Am Soc Hypertens* 2009;3:260-266.

C-reactive protein (CRP) is a recognized marker of inflammation, and is linearly associated with acute cardiovascular endpoints (e.g., MI, stroke). Whether this association is causal, concomitant, or consequent remains a matter of great debate. Indeed, even for advocates of the "CRP-leads-to-CVD events" hypothesis, it remains to be determined whether interventions which specifically lower CRP reduce events, and if so, whether event reduction is secondary to CRP reduction, or another cotherapeutic effect (i.e., as in statin therapy, wherein CRP is reduced, but so is LDL).

Hypertension is recognized to be the most important modifiable risk factor for cardiovascular disease. Different classes of antihypertensive therapy might have different effects upon CRP. To address this, a subgroup of the Genetic Epidemiology Network of Arteriopathy study group was analyzed. In this population, 662 subjects who were on monotherapy for hypertension (HTN) had their CRP measured. After adjustment for a variety of other factors (e.g., age, gender, BMI, smoking, diabetes), there were distinct differences in mean CRP depending upon which class of HTN monotherapy was being used. Overall, CRP levels were lowest in persons on inhibitors of the renin-angiotensin-aldosterone group (e.g., ACE inhibitor, ARB) and highest in the group on diuretics.

Current expert opinion suggests that simple blood pressure reduction is the primary effector of CV risk reduction, regardless of therapeutic class. The debate about whether therapeutic side-stream characteristics (e.g., class of agent, activity upon the renin-angiotensin-aldosterone system, metabolic effects) are important in selection of treatment will likely gain further fuel by these observations that various classes of HTN treatment differ in their effect upon the inflammatory marker CRP. ■

Clinical Briefs in Primary Care is published monthly by AHC Media LLC.

Associate Publisher: Coles McKagen. **Editor:** Stephen Brunton, MD. **Senior Managing Editor:** Paula Cousins. This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

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SSRIs and Pregnancy: Increase in Septal Heart Defects

In this issue: Depression and pregnancy, new vaccine recommendations from the CDC, corticosteroids and/or antivirals for Bell's palsy, rasagiline and Parkinson's disease, and FDA Actions.

Use of SSRIs during pregnancy

Depression is common in pregnancy, affecting up to 20% of women, with about 13% taking an antidepressant during pregnancy. A new study from Denmark suggests that use of sertraline (Zoloft®) and citalopram (Celexa®) by mothers during pregnancy is associated with an increased risk of septal heart defects in their children. Researchers utilized the Danish nationwide registry to review nearly 500,000 births from 1996 to 2003. Selective serotonin reuptake inhibitors (SSRIs) in general were not associated with major malformations, but were associated with septal heart defects. Among the individual drugs, sertraline conveyed the highest risk (odds ratio [OR], 3.25; confidence interval [CI], 1.21-8.75), followed by citalopram (OR, 2.52; CI, 1.04-6.10). Use of more than one SSRI was associated with an OR of 4.70 (CI, 1.74-12.7). The absolute prevalence of septal heart defects was 0.5% among unexposed children, 0.9% among children whose mothers received any SSRI, and 2.1% among children whose mother were prescribed more than one SSRI (*BMJ* 2009:339:b3569; Epub ahead of print 23 Sept 2009). Significant in this study was the low overall rate of heart defects and the lack of association of heart defects with paroxetine (Paxil®) or fluoxetine (Prozac®), although the authors consider this a "class effect," and the greatest risk was noted if more than one drug was used during pregnancy. ■

CDC issues new vaccine recommendations

The Centers for Disease Control and Prevention has recently revised several vaccine recommendations:

Quadravalent meningococcal conjugate vaccine. The Advisory Committee on Immunization Practices (ACIP) is recommending revaccination of persons at prolonged increased risk for meningococcal disease. In a statement in the September 25th *Morbidity and Mortality Weekly* Report, ACIP is recommending that persons with increased susceptibility to meningococcal disease, such as those with persistent complement component deficiencies, functional asplenia, prolonged exposure such as those traveling to or living in nations where the disease is epidemic or hyperendemic, should receive a booster with the quadravalent meningococcal conjugate vaccine 5 years after their previous vaccination if they received it at age 7 or older. Children who received the first vaccine between ages 2 and 6 should be revaccinated after 3 years. Those who remain at high risk should continue to be revaccinated every 5 years. The recommended booster vaccine is the MCV4 vaccine (Menactra®).

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

Haemophilus influenzae *type b vaccine.* The FDA recently approved Hiberix® for *Haemophilus influenzae* type b (Hib) ending a prolonged shortage of the Hib vaccine. Hiberix is approved as a booster for children ages 15 months to 4 years who have received a primary series of shots. The Centers for Disease Control and Prevention has now issued recommendations that the vaccine can be given as early as age 12 months to facilitate timely booster vaccination. Children who missed a booster because of the recent shortage should receive a booster with any of the Hib vaccines, including Hiberix, at the earliest opportunity.

Hepatitis A vaccine. Hepatitis A vaccine is now recommended for all close household contacts and international adoptees when the children are from intermediate-risk or high-risk areas, with an initial dose being given at least 2 weeks before the child's arrival.

Quadravalent human papilloma virus vaccine. In related news, an FDA advisory panel is recommending that the quadravalent human papilloma virus vaccine (Gardasil®) be approved for males ages 9-26 to prevent genital warts. The vaccine is currently approved only for females in that age group. Meanwhile, the same FDA advisory panel has endorsed the approval of GlaxoSmithKline's Cervarix®, a bivalent HPV vaccine which targets HPV 16 and HPV 18, leading causes of cervical cancer. If approved it would also be recommended in women ages 10-25. The new vaccine protects against 2 of the HPV strains covered by Gardasil, but also contains an adjuvant, which is designed to enhance the immune system's response to these HPV strains. Whether this imparts clinical difference is yet to be seen. The FDA is yet to act on the advisory committee's recommendations. ■

Bell's palsy: Corticosteroids and/or antivirals?

For treatment of Bell's palsy, corticosteroids with or without antivirals have been the subject of much debate. A new meta-analysis suggests that combination therapy may lead to better outcomes. The review included 18 trials with 2786 patients. The outcomes were unsatisfactory facial recovery at 4 months, unsatisfactory short-term recovery, synkinesis and autonomic dysfunction, or adverse effects. Combination therapy with corticosteroids and antivirals resulted in slightly better outcome than steroids alone ($P = 0.05$). Antiviral agents alone did not show a benefit (*JAMA* 2009;302:985-993). At least one source (UpToDate) recommends a typical treatment regimen for Bell's palsy of prednisone 60-80 mg per day along with valacyclovir 1000 mg three times a day for 1 week. ■

Rasagiline and Parkinson's disease

Does rasagiline slow the progression of Parkinson's disease? A recent study suggests lower doses of the drug may be beneficial. In this multinational study, 1176 subjects with untreated Parkinson's disease were randomized to rasagiline 1 mg or 2 mg per day for 72 weeks or placebo for 36 weeks followed by rasagiline for 36 weeks. Disease progression was rated on a standard rating scale. Patients who were started at baseline on rasagiline 1 mg met all endpoints in the primary analysis: a slower rate of worsening between weeks 12 and 36 ($P = 0.01$), less worsening of the score between baseline and week 72 ($P = 0.02$), and non-inferiority between weeks 48 and 72 ($P \leq 0.001$). Interestingly, all 3 endpoints were not met with the higher dose of 2 mg per day. The authors conclude that early treatment with rasagiline at a dose of 1 mg per day provided a possible disease-modifying effect, but suggested the results must be interpreted with caution (*N Engl J Med* 2009;361: 1268-1278). Although the findings of this paper are somewhat confusing, it offers some hope since there is currently no effective therapy to slow or stop disease progression in Parkinson's disease. ■

FDA Actions

The FDA has approved asenapine (Saphris®) for the treatment of schizophrenia and bipolar I disorder in adults. The drug is approved for first-line treatment of both conditions. Schering-Plough provided the agency with safety data in 4500 patients, some of whom were treated for more than 2 years. Like other antipsychotics, asenapine will carry a warning regarding increased mortality in elderly patients with dementia-related psychosis. The drug is expected to be available in the fourth quarter of 2009.

The FDA has lowered the approved age limit for levocetirizine (Xyzal®) to 6 months for children with chronic hives and perennial allergic rhinitis and 2 years for children with seasonal allergic rhinitis. Previously the drug had been approved for children 6 years and older. Levocetirizine is marketed by UCB and Sanofi Aventis. ■