Prevention of Migraine in Women Throughout the Life Span

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Migraine is a common disorder in women. The 1-year prevalence of migraine is 18% in women compared with 6% in men. Migraine most commonly occurs during the reproductive years, affecting 27% of women 30 to 49 years of age. The predominance of this disorder and its social, functional, and economic consequences make migraine an important issue in women's health. The hormonal milieu has a substantial effect on migraine in women. An understanding of these hormonal influences in the various stages of life in females is essential to the management and prevention of migraines. This article reviews migraine prevention strategies with an emphasis on specific therapies for each stage of a woman's life.

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COC = combined oral contraceptive; EE = ethinyl estradiol; HCl = hydrochloride; MM = menstrual migraine

Migraine is a common disorder in women, more common than diabetes mellitus, osteoarthritis, or asthma. Most of the 28 million Americans who have migraine are female,[1] with a 1-year migraine prevalence of 18% in females compared with 6% in males older than 12 years. In the United States alone, an estimated 112 million bedridden days per year are attributed to this disorder. Annual direct and indirect costs of migraine are estimated at $13 billion.[1]

Migraine most commonly occurs during the reproductive years, affecting 27% of women 30 to 49 years of age.[2] During these years, women are building both their families and their careers. The predominance of this disorder in reproductive-age women and its associated social, functional, and economic consequences make migraine management an important issue in women's health.

As women progress through the life stages, the hormonal milieu has a substantial effect on migraine. Menstruation, pregnancy, oral contraception, menopause, and hormone therapy influence its incidence and management. Thus, a thorough understanding of these hormonal influences is essential to the management of migraine in women. This article reviews preventive strategies with an emphasis on specific therapies for each stage of a woman's life.

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GENERAL PRINCIPLES OF PREVENTIVE THERAPY FOR MIGRAINE

The US Headache Consortium has outlined circumstances warranting preventive treatment for patients with migraine (Table 1).[3] Nonpharmacological strategies always form the foundation of a preventive treatment plan. Patients should be instructed to avoid migraine triggers (Table 2),[4,5] adopt a healthy lifestyle that includes regular sleep and exercise, and use nonpharmacological means of migraine reduction such as relaxation and biofeedback. Preventive medications are prescribed regularly to reduce the frequency, duration, and severity of anticipated attacks; to decrease the use of abortive medication; and to optimize the patient's ability to function.[3] The effectiveness of some therapies has been confirmed in multiple well-designed trials, and other treatments have been recommended by the US Headache Consortium in the absence of relevant randomized controlled trials (Table 3).

When selecting preventive therapies, physicians should consider the evidence-based efficacy of the agent, medications used previously, patient preference (eg, weight loss or gain, sedation), cost of the drug, and potential therapeutic opportunities to treat migraine and comorbid conditions with a single drug (eg, hypertension and migraine treated with a β-blocker).[1,12]

All medications should be initiated at a low dose and increased slowly until the effective or maximum dose is achieved or intolerable adverse effects develop. Each treatment option should be given a full therapeutic trial of 2 to 6 months. Efficacy, defined as a greater than 50% reduction in the frequency of headaches,[4] is often obtained in 4 weeks, but the full effect may not be realized for 3 months. About 50% of patients do not respond adequately to the initial preventive medication.[12] Having the patient keep a continuous diary of the frequency, severity, and duration of migraine attacks during treatment will help evaluate the effectiveness of the preventive method. A diary can be downloaded from the Web site of the American Council for Headache Education (www.achenet.org).

A combined approach using acute and preventive treatment increases the likelihood of long-term benefit. Preventive treatment may reduce the incidence of and vulnerability to attacks, and acute treatment aids in reducing migraine-related disability during attacks. The overuse of combination analgesics, opioids, ergot alkaloids, and/or triptans for acute migraine attacks may cause medication-overuse headaches. The beneficial effect of preventive medications can be abolished during the periods of symptomatic treatment abuse. However, the benefit can be regained after successful termination of this behavior. Clinicians must be aware of the potential for overuse of acute treatment and strictly limit its use to no more than 9 days a month on average. With a decrease in the need for acute treatment, preventive medications greatly decrease the incidence of medication-overuse headaches.

TABLE 1. **Circumstances Warranting Preventive Treatment for Migraine**

Recurring migraines that interfere substantially with patients' daily routines despite acute treatment (eg, ≥2 attacks per month that produce disability lasting ≥3 d)
Frequent headaches (≥2 per wk)
Contraindication to, failure of, or overuse of acute therapies
Adverse events with acute therapies
Patient preference for preventive vs abortive therapies (eg, cost, convenience, or effectiveness)
Presence of uncommon migraine conditions, including hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction (to prevent neurologic damage)

Data from Ramadan et al.[3]

MIGRAINE IN CHILDHOOD AND ADOLESCENCE

The characteristics and epidemiology of migraine in children and adolescents differ from those in adults. In young children (4-7 years), boys are more likely to have migraines than are girls.[7] By puberty, female migraineurs outnumber males 3 to 1.[7] Compared to migraines in adults, those in children are generally shorter in duration (1-48 hours vs 4-72 hours), tend to peak in intensity more quickly (often within 1 hour), and may be bilateral rather than unilateral.[7] Younger children may experience migraine variants such as benign paroxysmal vertigo, paroxysmal torticollis, cyclic vomiting, hemiplegic migraine, basilar migraine, or acute confusional migraine.[1] Children and adolescents are more likely to experience migraines on weekdays during school hours than at other times.[2]

In general, the approach to pediatric migraine is similar to but more conservative than that for adult migraine. Prevention should focus initially on lifestyle and behavioral changes. Parents and patients alike should learn to identify and avoid migraine triggers (Table 2). Stress plays a major role in triggering migraines in children and adolescents, and biofeedback and stress management techniques can be effective in children as young as 8 years.[7]

Despite conservative measures, roughly one third of pediatric migraineurs require periodic courses of daily preventive medication.[8] However, little published evidence supports the use of preventive medications in children, partly because of the high placebo response rate in pediatric patients enrolled in trials. Current practices are therefore based mainly on anecdotal experience or reported usefulness in adult trials. As in all stages of life, age and comorbid conditions must be considered when choosing prophylactic medications for young patients (Table 3).[7] For children younger than 6 years, the antihistamine cyproheptadine has been somewhat helpful, but it is less effective in older children.[7] Topiramate, with its side effect of weight loss, may be a preferred preventive choice for obese adolescents.[2] The preventive approach to migraine in children and adolescents is similar for boys and girls until puberty. The substantial increase in the prevalence of migraines at menarche requires more sex-specific approaches to prevention.

TABLE 2. **Common Migraine Triggers**

Chronobiologic
Schedule change
Sleep (too much or too little)*
Dietary
Additives
Alcohol*
Caffeine*
Certain foods
Fasting or skipping meals*
Hunger
Environmental factors
Altitude
Light glare or visual stimuli
Odors
Weather change
Head or neck pain
Trauma
Other causes
Hormonal changes
Menopausal fluctuations
Menstruation†
Medications
Prescription
Nonprescription
Physical exertion
Exercise
Sexual activity
Stress and anxiety†

*Trigger so common that all migraineurs should be advised to avoid it.
†Common powerful trigger that affects many women with migraine.
Modified from Table 9-11, from *Wolff's Headache and Other Head Pain*, edited by SD Silberstein, Dalessio, e, copyright © 2001, 1993 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.[4]
Data from Martin and Behbehani.[5]

TABLE 3. **Medications and Recommended Doses for Prevention of Migraine***

Agent	Quality of evidence in adult studies†	Recommended dose		Remarks
		Adult	Child (age [y])	
Phenobarbital	NR	NGU	1 mg/kg/d (0-2)	None
Serotonin antagonists				
Cyproheptadine HCl	C	NGU	0.25-1.5 mg/kg/d (2-5)	May cause weight gain and fatigue
β-Blockers				
Propranolol HCl‡	A	SD: 40-80 mg/d MD: 320 mg/d	1-3 mg/kg/d, divided into 2-3 doses (>6)	May help with coexisting panic attacks, anxiety, or essential tremor; when used with rizatriptan benzoate, reduce dose of rizatriptan
Timolol maleate‡	A	SD: 10 mg/d MD: 30 mg/d	NGU	None
Atenolol	B	SD: 50 mg/d MD: 100 mg/d	NGU	None
Metoprolol tartrate	B	SD: 50 mg/d MD: 200 mg/d	NGU	None
Nadolol	B	SD: 20 mg/d MD: 160 mg/d	NGU	None
Tricyclic antidepressants				
Amitriptyline HCl	A	SD: 10 mg/d MD: 150 mg/d	0.25-1 mg/kg/d or divided into 2 doses (>6)	May cause long-term weight gain; often causes anticholinergic adverse events; may lower seizure threshold in patients with frequent seizures; useful for coexistent depression or tension-type headache
Nortriptyline HCl	C	SD: 10 mg/d MD: 100 mg/d	0.25-1 mg/kg/d or divided into 2 doses (>6)	Better tolerated than amitriptyline; less sedation
Protriptyline HCl	C	SD: 15 mg/d MD: 40 mg/d	NGU	Weight gain less common than with other tricyclic antidepressants
Doxepin HCl	C	SD: 10 mg/d MD: 150 mg/d	NGU	None
Calcium channel blockers				
Verapamil HCl	B	SD: 120 mg/d MD: 320 mg/d	4-5 mg/kg/d, divided into 1-3 doses (>6)	Constipation is common; do not use if conduction block is present; alternative to β-blockers in athletes; recommended for prolonged or atypical migraine aura
SSRIs				
Paroxetine HCl	C	Efficacious dose not established	10-20 mg/d (>6)	May be beneficial if migraine occurs with anxiety or depression
Fluoxetine HCl	B	SD: 10 mg/d MD: 80 mg/d	NGU	Insomnia, fatigue, tremor, and abdominal pain are common adverse effects
Neuromodulators				
Divalproex sodium,‡ valproic acid (FDA approved only for adults)	A	SD: 250 mg bid MD: 1 g/d	10-30 mg/kg/d, divided into 2-3 doses (>6)	Monitor liver function, especially for first 6 mo of treatment; possible pancreatitis; avoid abrupt cessation; potential fetal risk of neural tube defects; may increase androgen levels and PCOS; may increase appetite
Gabapentin	B	Day 1: 300 mg Day 2: 300 mg bid Day ≥3: 300 mg tid MD: 2400 mg/d	10-20 mg/kg/d, divided into 2 doses (>6)	None
Topiramate‡ (FDA approved only for adults)	A	Wk 1: 25 mg qhs Wk 2: 25 mg bid Wk 3: 25 mg qam; 50 mg qhs Wk 4: 50 mg bid	0.25-1 mg/kg/d, divided into 2 doses (>6)	May cause weight loss, fatigue, poor concentration, nausea, tingling of extremities; increasing dosage slowly minimizes adverse effects
NSAIDs	B-C	Doses vary	Doses vary	Various forms used; potential for overuse and rebound headaches; used mainly for menstrual migraine
Miscellaneous				
Lisinopril	NR	SD: 10 mg/d MD: 40 mg/d	NGU	May be effective
Magnesium	B	360-400 mg/d MD: 600 mg/d	NGU	Use of nonchelated formulation associated with severe diarrhea; may be useful in patients with PMS
Vitamin B_2 (riboflavin)	B	400 mg/d	NGU	None
Feverfew	B	10-30 mg/d	NGU	Withdrawal may be associated with increased headaches
Botulinum toxin type A injections	NR	25-75 U IM or SC	NGU	Emerging evidence of efficacy

*bid = 2 times a day; FDA = Food and Drug Administration; HCl = hydrochloride; IM = intramuscularly; MD = maximum dose; NGU = not generally used; NR = not rated; NSAIDs = nonsteroidal anti-inflammatory drugs; PCOS = polycystic ovary syndrome; PMS = premenstrual syndrome; qam = once daily, every morning; qhs = once daily at bedtime; SC = subcutaneously; SD = starting dose; SSRIs = selective serotonin reuptake inhibitors; tid = 3 times a day.

†A = multiple well-designed randomized clinical trials, directly relevant to recommendation, yielded consistent pattern of findings; B = some evidence from randomized clinical trials supported recommendation, but scientific support was not optimal; C = US Headache Consortium achieved consensus on recommendation in absence of relevant randomized controlled trials.

‡FDA approved for migraine prophylaxis.

Data from references 1, 3, 6-11.

REPRODUCTIVE YEARS

During the reproductive years, headaches in women are commonly associated with menses, pregnancy, and use of combined oral contraceptives (COCs). Thus, preventive strategies should be tailored to specific reproductive stages.

Menstrual Migraine

About 60% of female migraineurs have migraines associated with their menstrual cycle, making menstruation one of the most common triggers.[1,13] Migraine attacks without aura are more likely to be associated with the menses than are migraines with aura.[14] Menstrual migraine (MM) is not recognized by the International Headache Society as a specific headache diagnosis. Nonetheless, in an appendix to its new classification system, the society suggested research criteria for MM as follows: (1) *pure MM*—attacks occur exclusively from 2 days before menses to the third day of menstruation (days –2 to +3) in at least two thirds of the menstrual cycles and (2) *menstrually related migraines*—attacks occur during days –2 to +3 in at least two thirds of the cycles and also at other times.[15]

Menstrual migraine is thought to be triggered by the decline in estrogen levels that occurs in the late luteal phase of the cycle.[16] Unlike other forms of migraine prevention, prophylaxis for pure MM involves treatment only during the period of vulnerability around the menses. Regular cycles with headaches timed predictably around the menses are required for this method of "miniprophylaxis." Agents with documented efficacy in miniprophylaxis include nonsteroidal anti-inflammatory drugs, ergot alkaloids, and triptans (Table 4).[1,3,17-20] For women who require continuous daily preventive therapy, menstrually related migraines may respond to an increase in the dose of their existing prophylactic medicine during the vulnerable time around the menses.[19] Some patients with severe MM have an improved response to miniprophylaxis while receiving chronic prophylactic medication.

Oral Contraceptives

Many women with MM also take COCs, which can unpredictably induce, alter, or alleviate migraines. The normal decline in endogenous estradiol concentration in the late luteal phase of the natural menstrual cycle is equivalent to a 20- to 25-μg decline in synthetic ethinyl estradiol (EE).[13] Thus, no COC will prevent MM in a woman who has headaches during her natural cycle because even the lowest-dose medication produces a decline equivalent to 20 μg of EE premenstrually. If use of COCs exacerbates migraines throughout the cycle, the initial strategy should be to lower the estrogen content to 20 μg of EE. Persistent headaches despite this intervention may necessitate discontinuing COCs in these patients.[20] When a woman experiences prolonged aura, focal neurologic symptoms different from those of her typical aura, or a sudden prolonged headache, use of COCs should be discontinued, and possible secondary causes of headache should be explored.[16]

TABLE 4. **Preventive Treatment of Menstrual Migraine***

Miniprophylaxis
Naproxen sodium, 550 mg bid for 2 wk, starting 1 wk before PDM and continuing for 1 wk after first day of menses
Magnesium, 360 mg/d for 2 wk, starting 2 wk before PDM
Ergotamine tartrate (1 mg) plus caffeine (100 mg) (Cafergot, Geneva Pharmaceuticals, Inc, Broomfield, Colo), 1 tablet for 5 d, starting 2 d before PDMM
Frovatriptan succinate, 2.5 mg bid for 6 d, starting 2 d before PDMM
Naritriptan hydrochloride, 1 mg bid for 5 d, starting 2 d before PDMM
Sumatriptan succinate, 25 mg tid for 5 d, starting 2 d before PDMM
Long-term prevention
Standard prevention medications on daily basis
Increase long-term medication dose perimenstrually if needed
Hormonal manipulation
Extended-cycle use of COCs (preferably monophasic, low-dose EE)
Add-back estrogen therapy during placebo week of COCs
0.9 mg conjugated equine estrogen per day (start first day of inert pills)
0.1 mg estradiol transdermal patch (apply 2 d before beginning inert pills and continue throughout placebo week)

*bid = twice daily; COCs = combined oral contraceptives; EE = ethinyl estradiol; PDM = predicted day of menses; PDMM = predicted day of menstrual migraine; tid = 3 times a day.
Data from references 1, 3, 17-20.

Migraineurs taking COCs often experience headaches during the placebo week. These migraines may respond to alternative hormonal approaches. Limiting the premenstrual decrease in estradiol equivalent to 10 μg of EE or less may prevent MM associated with the placebo week of COCs. Calhoun[13] prevented this decline by giving patients who were taking COCs 0.9 mg of conjugated equine estrogens on cycle days 22 to 28 (ie, the placebo days). Other ways to limit this decline include use of transdermal estrogen (gel or patch) during the placebo week or long-cycle use of COCs. Monophasic COCs may be used safely in long-cycle regimens by skipping the placebo week for 2 to 4 cycles.[20] One packaged COC (Seasonale, Duramed Pharmaceuticals, Inc, Cincinnati, Ohio) extends the cycle to 91 days. Triphasic preparations are not recommended for long-cycle use. Commercial formulations that add 10 μg of EE after 2 days of inert pills (eg, Mircette or Kariva, Barr Pharmaceuticals, Inc, Pomona, NY) do not prevent the sudden decline in estrogen on day 22 and thus offer no advantage over other COCs in prevention of MM.[13]

Stroke risk for migraineurs taking COCs has been a concern for prescribing practitioners because both migraine and COCs increase risk. For women younger than 45 years, the

absolute risk of ischemic stroke is low (5-10 per 100,000 women-years). Although the odds ratio for ischemic stroke in migraineurs is 3 to 6, the absolute risk for ischemic stroke remains low at 17 to 19 per 100,000 women-years. Use of COCs by migraineurs increases the odds ratio for ischemic stroke to 5 to 17. A review by the International Headache Society Task Force on Combined Oral Contraceptives and Hormone Replacement Therapy found no contraindication to use of COCs containing less than 50 μg of EE for women with migraine without aura who have no other risk factors for ischemic stroke.[21] However, migraineurs with aura or other risk factors for stroke (Table 5) should be assessed individually for appropriateness of COC use. Because the combination of cigarette smoking, COCs, and migraine increases the risk of stroke 34-fold, COCs should not be used by migraineurs who smoke.[21-23]

TABLE 5. **Additional Risk Factors for Ischemic Stroke in Women With Migraine Who Use Combined Oral Contraceptives**

Age >35 y
Ischemic heart disease or cardiac disease with embolic potential
Diabetes mellitus
Family history of arterial disease at <45 y
Hyperlipidemia
Hypertension
Migraine aura
Body mass index >30
Smoking
Systemic diseases associated with stroke (eg, sickle cell disease or connective tissue disease)

Data from Bousser et al.[21]

Pregnancy

Migraine frequency and severity vary during pregnancy. By the end of the first trimester, 50% to 80% of pregnant migraineurs note a decrease in the frequency of attacks; a small percentage experience worsening or onset of migraines.[16] Secondary causes of headache should be considered when a woman presents with a severe headache for the first time during pregnancy.[2] All pregnant migraineurs should strictly avoid migraine triggers (Table 2).

In general, preventive medications should be avoided in pregnant patients because of the potential for teratogenicity. Category C medications (eg, propranolol hydrochloride [HCl], verapamil HCl, or topiramate) are a last resort for severe, frequent, refractory migraines if benefit outweighs risk for both mother and fetus. Medications that should not be prescribed for pregnant women include valproic acid and divalproex sodium (teratogenic category D drugs) and ergot derivatives (category X).[1,2,9,24]

MENOPAUSE

Migraine in Menopausal Transition and Early Menopause

Fluctuating hormone levels may exacerbate migraine during perimenopause, making the menopausal transition particularly challenging for female migraineurs. The menopausal transition is defined as the time before the final menstrual period when there is variability in the menstrual cycle. Menopause, defined as the cessation of menses for 12 months, occurs at a median age of 51 years. Perimenopause includes the transitional years as well as the first year after menopause.[25] The hormonal basis for migraines during the transitional years makes them amenable to management with hormonal manipulation. Long-cycle or continuous-use low-dose COCs in perimenopausal migraineurs may provide both necessary contraception and migraine control.[20]

After natural menopause, migraines improve in about two thirds of women as hormone levels stabilize.[1] Postmenopausal migraine may be exacerbated or relieved by hormone therapy. When hormone therapy is used for menopausal symptoms, a continuous low-dose estrogen regimen is less likely to exacerbate migraines.[23] Migraines worsen in two thirds of women after surgically induced menopause. Therefore, surgical induction of menopause should not be proposed as a way to prevent migraines.[1] For women experiencing ongoing migraines after menopause, standard preventive medication should be selected on the basis of existing comorbid conditions (Table 3). Any new onset of severe headache after age 45 should be evaluated for secondary causes because migraine does not typically begin at this age.[23]

Migraine in Elderly Women

Migraine beginning after age 65 is extremely uncommon and warrants thorough investigation. Clinicians should be aware that as many as one third of all headaches in elderly women are due to secondary causes.[2] In this population, a careful history, physical examination, and consideration of more ominous causes should precede initiation of preventive therapy for migraines.

Migraine in elderly women may be accompanied by aura or may occur as recurrent attacks of painless aura. The syndrome of aura without headache (late-life migraine accompaniment) is easily confused with transient ischemic attacks (Table 6).[2] Comorbid conditions and polypharmacy make preventive therapy challenging in elderly women and highlight the importance of initial nonpharmacological preventive approaches. Migraine prevention in women with coronary artery disease is especially important because these patients must avoid acute treatment with triptans.[23] β-Blockers may be a first-line migraine prevention option in patients with cardiac disorders or hypertension but are contraindicated in those with asthma, chronic obstructive pulmonary disease, or hypotension. Tricyclic antidepressants are associated with

TABLE 6. **Distinguishing Features of Late-Life Migraine vs Transient Ischemic Attacks**

Type of feature	Migraine aura	Transient ischemic attack
Visual symptoms	Positive phenomena (eg, scintillating scotoma)	Negative symptoms (eg, loss of vision)
Onset	Gradual buildup	Abrupt
Progression	Sequential from 1 modality to another (eg, vision to speech)	Simultaneous appearance
Symptomatology	Repetitive attacks of identical nature	Variable symptomatology
Average duration	20-30 min	<15 min
Frequency	Flurry of midlife attacks common	Flurry of attacks uncommon
Association with headache	Followed by mild headache 50% of the time	Headache less frequent

Modified from Gladstone et al[2] with permission.

problematic adverse effects and are contraindicated in patients with arrhythmias or urinary retention. Nortriptyline HCl and desipramine HCl are preferable to amitriptyline HCl because they have fewer anticholinergic adverse effects. Valproic acid, divalproex, topiramate, and gabapentin are beneficial in migraine prevention in this age group but have considerable adverse effects. Although gabapentin has sedative effects, it may be preferred for patients with comorbid neuropathy. Botulinum toxin type A is being tested as a preventive therapy. Although currently no consistent evidence suggests that botulinum toxin is effective in migraine prevention, it has the potential to be especially important in the management of elderly patients with migraine because of its lack of systemic absorption and subsequent low adverse-effects profile.[2,6] As a general rule, lower doses of all prophylactic medications are used in elderly patients to avoid untoward effects.

CONCLUSION

Migraine affects many women throughout the life span, yet only 3% to 5% of them receive preventive therapy.[3] Preventive medications can effectively reduce resource utilization by decreasing the use of other migraine medications, the use of diagnostic tests, and visits to physician offices and emergency departments.[26] An understanding of the treatment options available for migraine prevention in women at various life stages can help physicians select appropriate prophylactic therapy.

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Questions About Migraine Prevention in Women

1. Which *one* of the following statements about migraine is *false*?
   a. In women, migraine is more common than diabetes, osteoarthritis, or asthma
   b. After age 12, females have a 1-year migraine prevalence that is 3 times that of men
   c. Migraines in women occur most commonly in the menopausal years
   d. In young children (4-7 years), migraines are more likely to affect boys than girls
   e. In the United States, annual direct and indirect costs associated with migraine are estimated at $13 billion
2. Which *one* of the following migraine characteristics is seen more commonly in adults than in children?
   a. Peak intensity occurring less than 1 hour after start of the migraine
   b. Variants such as paroxysmal torticollis and cyclic vomiting
   c. Bilateral throbbing headache
   d. Duration as long as 72 hours
   e. May respond to cryoheptadine
3. A 30-year-old woman taking a 30-µg COC is experiencing withdrawal migraines without aura during the placebo week. Which *one* of the following is *not* an appropriate preventive treatment option?
   a. Daily 0.9-mg conjugated equine estrogen during the placebo week
   b. Extended-cycle use of a monophasic COC
   c. Addition of a 0.1-mg estrogen patch during the placebo week
   d. Switch to a COC formulation that adds 10 µg of EE after 2 days of inert pills
   e. Switch to a 20-µg COC and, if withdrawal headache continues, add estrogen throughout the placebo week
4. The combination of migraine, COCs, and smoking increases the risk of stroke by which *one* of the following rates?
   a. 3-fold
   b. 5-fold
   c. 9-fold
   d. 34-fold
   e. 64-fold
5. Which *one* of the following statements about migraine during perimenopause is *true*?
   a. Migraine headaches worsen in two thirds of women after menopause
   b. Surgical induction of menopause will decrease migraines in most women
   c. New-onset headache after age 45 requires evaluation for secondary causes
   d. Long-cycle use of triphasic COCs is recommended for alleviation of migraines during perimenopause
   e. Perimenopausal migraines are well suited for miniprophylaxis

Correct answers:
1. *c*, 2. *d*, 3. *d*, 4. *d*, 5. *c*