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   (A) A meta-analysis suggests that the use of HRT for ≤5 yr during perimenopause does not increase the risk for thromboembolic events. (B) A study showed use of low-dose (<50 µg) estrogen patches in younger women who did not smoke did not increase the risk for stroke.
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   1. Polypharmacy occurs in ≤80% of migraine sufferers.
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   7. Study data show which of the following OTC formulas to be superior to 50 mg sumatriptan as determined by a score comprising the sum of pain intensity differences at 4 hr?
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   Answers to Audio-Digest Neurology Volume 02, Issue 19: 1-D, 2-C, 3-D, 4-B, 5-B, 6-D, 7-D, 8-A-C, 9-D, 10-D

Perimenopause and Headache

Jan Lewis Brandes, MD, MS, Assistant Clinical Professor of Neurology, Vanderbilt University School of Medicine, and Director, Nashville Neurology Group, TN.

Headache
To test online, go to www.audiodigest.org before listening.

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Educational Objectives

The goal of this program is to improve the management of migraine headaches among all faculty and members of the planning committee.

1. Summarize the effects of changing levels of estradiol on migraine headaches.
2. Determine whether patients’ migraine headaches are influenced by hormonal changes and whether hormonal therapy is appropriate.
3. Recognize the prevalence of self-medication with over-the-counter medications (OTCs) among patients with headaches and advise patients on the best use of these agents.
4. Evaluate the strength of the clinical data that support the efficacy of OTCs.
5. Identify and resolve the potential interactions of concern between triptans and other commonly used medications as well as drugs used for migraine prophylaxis.

Faculty Disclosure

In adherence to ACME Standards for Commercial Support, Audio-Digest Foundation requires all faculty members and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, the following has been disclosed: Dr. Brandes has received personal compensation for activities (specific nature of relationship undisclosed) with Advanced Bionics, Allergan, AstraZeneca, Endo Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceuticals, Johnson & Johnson, and Merck & Co, Pfizer, POZEN, sanot-arenets US, UCB SA, Vernalis; additionally, Dr. Brandes receives research support from Advanced Bionics, Allergan, Astrazeneca, Boston-Myers Squibb, Elan Corporation, Endo Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceuticals, Johnson & Johnson, Merck & Co, Novartis AG, Pfizer, POZEN, sanot-arenets US, UCB SA, Vernalis, and Winston Pharmaceuticals. Dr. Banks and the planning committee reported nothing to disclosed. In their lectures, Drs. Brandes and Banks present information related to the off-label or investigational use of a product, therapy, or device.
Biosimilar products are becoming a common practice worldwide, and their use has been shown to improve access and affordability of medications in several countries. However, the safety and efficacy of these products are critical considerations, and ongoing research is needed to ensure their continued use is safe and effective.
of new treatments that are effective in preventing headaches. These include coenzyme Q10, magnesium, and butterbur (MigreLief); vitamin B2, magnesium, Co-Q-10, and butterbur (Migravent). A meta-analysis of data from controlled trials showed that anticonvulsant medications could not protect against stroke in subsequent large trials; no clinical evidence supports strict contraindication of magnesium (Migralex) in patients with migraine.

**Drug Interactions:** Information is available at www.drugwatch.com. Pharmacodynamic and pharmacokinetic interactions may cause symptoms such as blood pressure, pulse; symptoms of nausea, diaphoresis, and sweating; or significant changes in express hypercoagulability:

**Female reproductive steroids and neuronal excitability:** Estradiol and levonorgestrel (Climara Pro), but avoid injectables in women with uterus; for menstrual migraine, maintenance of estrogen level between 50 to 70 pg/mL most protective (but too much, too little, or fluctuation can all cause problems). 2006; involves manifestations of central serotonin hyperstimulation, including neurocognitive changes (e.g., confusion, agitation), neurornuscular activation (e.g., hyperreflexia, hypertonia, rigidity), and autonomic hyperactivity (elevated blood pressure and pulse); look for tachycardia, tachypnea, and hyperreflexia; concern greater if patient has hypertension and indexed clinical load; diagnostic criteria include 

**Serotonin Syndrome:** Background: United States Food and Drug Administration (FDA) issued advisory (2006); involves manifestations of central serotonin hyperstimulation, including neurocognitive changes (e.g., confusion, agitation), neurornuscular activation (e.g., hyperreflexia, hypertonia, rigidity), and autonomic hyperactivity (elevated blood pressure and pulse); look for tachycardia, tachypnea, and hyperreflexia; concern greater if patient has hypertension and indexed clinical load; diagnostic criteria include 

**Clinical trials:** Serotonin syndrome adequate clinical trials; several OTCs approved for migraine; study found formulation of acetaminophen, aspirin, and caffeine. Excessive use may lead to pain relief than placebo within 2 hr and at all times; similar results observed from studies of ibuprofen (Advil Migraine) among patients with mild intermittent headaches (>66% of patients had relief within 2 hrs). Acetaminophen, aspirin, and caffeine (ASA) is sumatriptan in early treatment of migraine (ASSIST trial): used sum of pain intensity differences at 4 hr (SPD4) as end point; found AUC associated with > 90% relievers. Advise patients: data support use of OTCs in some patients if not used during a prior attack; use prescription medication and do not combine with other OTCs. Additional over-the-counter medications: include sinus medica- tions (may relieve symptoms caused by trigeminal activation and appear to relieve headache because of vasemotion; topical preparation (HeadOn); gauze leaf extract (Drink-A-Mine); small porous, tending to cause erythema; kudzu and other herbal teas; combination of aspirin and magnesium (Equate).

Over-the-counter preventive medications: 5-hydroxytryptophan (5-HTP); increases serotonin; coenzyme Q10 (Co-Q-10); reduces pain on movement; effective; few adverse results; mixed results; little evidence of melatonin reported successful with cluster headaches (possi- bly due to increased circadian rhythms). Combinations: also includes fever, vitamin B2, and magnesium (Migrelief), vitamin B2, magnesium, Co-Q-10, and butterbur (Migravent). Migraines: include feverfew, vitamin B2, and magnesium (Migrelief), vitamin B2, magnesium, Co-Q-10, and butterbur (Migravent). Migraine: include feverfew, vitamin B2, and magnesium (Migrelief), vitamin B2, magnesium, Co-Q-10, and butterbur (Migravent).

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Incidence: incidence: analysis from Merck-Medico database during 2000 to 2001 (65 million covered lives) showed >240,000 patients filled prescriptions 24+ times over 6 mo; among those, 800,000 had filled prescriptions for SSRIs; extrapolations of data to population estimates suggests 185,000 patients used triptans and serotonin agents (e.g., 81 million patient-months of exposure). Incidence of serotonin syndrome among patients treated with serotonin agents is 0.03%; serotonin syndrome occurs more often in monotherapy with SSRIs than with combination therapy (over 1000 patient-months; <0.002% of episodes life threatening). Pathophysiology: serotonin syndrome mediated by 5-hydroxytryptophan (5-HTP), receptors, and might occur with other serotonergic agents and agents acting at 5-HT receptors, suggesting triptans should not affect serotonin syn- drome; no clinical evidence supports strict contraindication of triptans in patients with migraine. Small studies, taking for prevention agents but liability rates high; comorbidities of anxiety and depression prevalent in population with migraine, and need for both types of medica- tion: Symptons: occur when patients overdose on triptans; typical of serotonin syndrome: headache worse; autonomic dysfunction; fever; nausea; diarrhea; agitation, sweating, nausea, and restlessness probably dizziness; no clinical evidence supports strict contraindication of magnesium (Migralex) in patients with migraine.

**Acknowledgements**

Dr. Brandes and Banks spoke at Headache Update 2010, held July 12-16, 2010, in Lake Vista, FL, presented jointly by the Di- agnosis, CME and Research, Educational Foundation, Diamond Headache Clinic Research and Educational Foundation, visit http://www.dhc-fdn.org. The Audio-Digest Foundation thanks the speak- ers and the sponsors for their cooperation in the production of this program.

**Suggested Reading**

Allais G et al: Oral contraceptives in migraine therapy. Neurol 52 (5):1193-1194, 2005. 2005. 2006; involves manifestations of central serotonin hyperstimulation, including neurocognitive changes (e.g., confusion, agitation), neurornuscular activation (e.g., hyperreflexia, hypertonia, rigidity), and autonomic hyperactivity (elevated blood pressure and pulse); look for tachycardia, tachypnea, and hyperreflexia; concern greater if patient has hypertension and indexed clinical load; diagnostic criteria include thrombus and Hunter (Hunter criteria require either inducible or spontaneous life threatening). Cases reported: serotonin syndrome reported in monotherapy with SSRIs, SNRIs, tricyclics, and monoamine oxidase (MAO) inhibitors. 27 cases reported in which serotonin syndrome associated with recent significant changes in dose and occurred in patients using triptan plus SSRIs and other serotoner- 

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**MAO inhibitors:** rarely used, but possible to cautiously combine subcutaneous MAO inhibitors with ergotamines, but avoid patients who are taking multiple subcutaneous medica- tions; advise patients to reduce dose of topiramate or use other form of contraception or other hormonal mediation.
HEADACHE

To submit a test form by mail or fax, complete Pretest section listening.

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7. Study data show which of the following OTC formulations to be superior to 50 mg sumatriptan as determined by a score comprising the sum of pain intensity differences at 4 hr?
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8. Which of the following drugs or drug classes may produce interactions of concern with triptans?
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   (B) Monopropaline
   (C) Monoamine oxidase inhibitors
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9. Serotonin syndrome occurs more often with high-dose monotherapy with SSRIs (0.9 to 0.9 mg cases per 1,000 patient-months) than with SSRIs combined with triptans
   (A) True (B) False

10. Which of the following combinations of triptans and β-blockers requires changes in the recommended dose of triptan?
    (A) Serotonin and propranolol
    (B) Sumatriptan and metoprolol
    (C) Zolmitriptan and propranolol
    (D) Rizatriptan and propranolol

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Perimenopausal Headache

Jim Lewis Brandes, MD, MS, Assistant Clinical Professor of Neurology, Vanderbilt University School of Medicine, and Direc-
ktor, Nashville Neuroscience Group, TN

Hormones and migraine: levels of estradiol higher in perimenop-
use; women enter perimenopause at average of 47 yr of age; ovarian failure may occur earlier if woman has utens removed, premature menopause may occur at 20 to 30 yr of age; fluctua-
tion of estradiol levels affects hypereosinophilia in brain, all de-
developed associated with migraine lead to cortical hyperteresiety; estrogen receptors may increase in number, eg, in brainstem and peri- aqueductal gray (where pain gated and controlled and inhib-
itory pathways located); after menopause, women with hormonally 
favored patterns of migraine improve

Patient Examination

Determine perimenopausal status: evaluate age, menstrual his-
tory, and other symptoms; medical tests least useful because of variability from day to day

History of headache patterns: may suggest options for therapy; ask about headaches during childhood, age at first menstruation, headaches (even mild) at time of menstrual period, or menstrual cramping (which may suggest endometriosis and influence treatment choices)

Oral contraceptives and pregnancies: if oral contraceptives used, ask when started, occurrence of headaches, reasons for stop-
ping, and whether headaches increased by stopping; ask about headaches during pregnancies and breastfeeding; if oral contra-
ceptives helpful in past, continuous oral contraceptive regimen may help headaches during transition to menopause; if oral con-
traceptives worsened headache in past, low-dose hormone re-
placement therapy (HRT) may help; ask about history of infertility and response to drugs, eg, clomiphene (Clomid, Milophene, or Se-
ropene) or endometriosis and response to leuprolide (Lupron)

Hormonal Therapy

Background: evaluate influence of hormonal changes on head-
aches; identify risk factors, eg, osteopenia, family history of is-
toporosis; consider hormone manipulation for women whose headaches associated only with breakthrough bleeding; if non-
 hormonal attacks occur in addition to hormonally influenced 
headaches, consider dual or conventional therapy; data from tri-
als of frovatriptan for short-term prevention of menstrual mi-
graines published, but frovatriptan not approved for this indication

Patient selection: consider HRT for women at high risk for colon cancer or fractures; if symptomatic women, some who had premenstrual syndrome worsening given HRT, impor-
tant for patient to record headache patterns in diary to evaluate effects of hormone manipulation on headaches

Hysterectomy: headaches may improve, but hysterectomy to treat headaches not warranted; changes in brain suggest loss of sero-
tonicergic cells in dorsal raphe as women age; study of migraine in 
physiologic menopause found 66% of women improve ≥1 yr after last period, but 66% of those who undertook surgical meno-
pause worsen; important to plan for effects of hysterectomy in 
women with migraine; another study that looked at episodic mi-
graine found only 13% of postmenopausal women had head-
ache; few data on effects of perimenopause on chronic migraine; advise women that very little understood about changes in hypersexestrogery as related to pain perception; study found women on HRT had lower thresholds and tolerance for thermal pain, but women not on HRT did not differ from men in their response to thermal pain

Concerns about hormone replacement: many women on conjugated estrogens and medroxyprogesterone (Prempro or Prem-
 phase) stopped abruptly after data from Women’s Health

Educational Objectives

The goal of this program is to improve the management of mi-
grave headaches and treatment of headaches in the context of 
the- counter medications (OTCs) among patients with mi-
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and Winston Pharmaceuticals. Dr. Banks and the planning committee 
reported nothing to disclose. In their lectures, Drs. Brandes and 
Banks present information related to the off-label or investiga-
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Faculty Disclosure