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Your postmenopausal patient reports a history of migraine

Would a trial of hormone therapy increase her risk of stroke?

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CASE Menopausal symptoms and a history of migraine with aura

Your new patient is a 52-year-old woman (G2P2) who reports a long history of two types of migraine: menstrually related migraine without aura and nonmenstrually related migraine with aura (usually involving visual scotomata). Other than the history of migraine, her health is good. Now postmenopausal, she has been referred to you by her primary care physician (PCP) for management of severe vasomotor symptoms and sleep disturbance.

Because of this patient's history of migraine, her PCP declined to prescribe oral contraceptives (OCs) in the past over concern

of increasing her risk of stroke. For her vasomotor symptoms, her PCP prescribed a trial of venlafaxine (Effexor) 75 mg daily, but her orgasms, which always had been difficult to achieve, became impossible. In addition, the patient began to perspire heavily unrelated to her hot flashes. As a result, she describes her mood as "terrible," her energy level as "miniscule," and she reports losing interest in sex completely ("I am just too tired"). She and her referring physician wonder whether it would be safe to try hormone therapy (HT).

A physical examination, including fundoscopic assessment, reveals no abnormalities. Her blood pressure is 126/70 mm Hg, and blood chemistry results, including C-reactive protein, 25-hydroxy vitamin D, a complete blood count, and lipid profile, are all normal.

Would you offer this patient the option of HT?

Migraine affects roughly twice as many women as men.¹ During the reproductive years, rapid fluctuations in ovarian hormones—both increases at midcycle and, to a greater extent, decreases during the premenstrual phase—are believed to be migraine "triggers." Women who experience menstrually related migraine before menopause typically have an increased risk of migraine during perimenopause, with a significant reduction of migraine symptoms following menopause.²

Side effects of SSRIs and SNRIs

Most providers are aware that selective serotonin reuptake inhibitors (SSRIs) cause sexual

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Dr. Kaunitz and Dr. Pinkerton provided peer review and comments for Dr. Simon's case study.

IN THIS ARTICLE

Migraine and the risk of stroke
page 20

Why hormone therapy may be appropriate
page 22

How I would manage this patient
page 22

CONTINUED ON PAGE 20

side effects in as many as 80% of users. There is a dose-related pattern to reports of sexual problems among SSRI users, with higher doses causing more problems. The most common sexual symptoms associated with SSRIs are delayed ejaculation and absent or delayed orgasm.³

What is not as widely known is that even serotonin-norepinephrine reuptake inhibitors (SNRIs) can cause sexual dysfunction. For example, in a prospective, multicenter study from Spain involving more than 1,000 outpatients, all of whom were taking an antidepressant, the overall rate of sexual dysfunction was 59%.⁴ Sexual dysfunction was most common among users of SSRIs and venlafaxine, an SNRI.⁵

Another common side effect of venlafaxine, sweating, is unrelated to hot flashes.⁵ So two of this patient's concerns—orgasmic difficulties and profuse sweating unrelated to hot flashes—may have been caused or worsened by her antidepressant.

Another nonhormonal option

In June 2013, the US Food and Drug Administration (FDA) approved **paroxetine mesylate** (Brisdelle), an SSRI, for the treatment of moderate to severe menopausal vasomotor symptoms. Because the drug is a strong CYP2D6 inhibitor, it should not be given to women taking another medication that is metabolized by CYP2D6—most notably, tamoxifen.

Preliminary data on this drug suggest that, at the recommended dose (7.5 mg/d), it has no effect on sexual function.⁶ For this reason, it is another option for our patient to consider.

Migraine and the risk of stroke

Migraine with aura has been associated with an increased risk of stroke and other cerebral vascular events,⁷ and that risk is further elevated in patients treated with OCs.⁸ Although migraine *without* aura also may be associated with an elevated risk of stroke, OCs do not further increase that risk.

DR. KAUNITZ *The elevated risk of stroke associated with use of OCs by women with migraine with aura appears to relate, in particular, to older, higher-dose OC formulations.^{9,10}*

Some practitioners assume that the data on the risk of stroke associated with OC use also applies to hormone therapy, but there is no evidence that HT, in which doses of estrogen are far lower than in OCs, increases the risk of stroke in migraineurs to any greater degree than would be expected in unselected populations (ie, as noted in the Women's Health Initiative, Nurses Health Study, or other large investigations). Therefore, HT would be an appropriate option for this patient if her very slight risk of stroke on HT would be acceptable to the practitioner and patient.

DR. PINKERTON *The route of administration is critical here. In relatively healthy postmenopausal women (average age, 63), combined continuous oral HT significantly increased the risk of stroke. After 3 years of use, the absolute risk was 18 cases of stroke per 1,000 HT users (95% confidence interval [CI], 14–23). And oral estrogen-only therapy increased the risk of stroke after 7 years of use, with an absolute risk of 32 cases per 1,000 HT users (95% CI, 25–40).¹¹*

The limited clinical evidence available on the effects of transdermal estradiol on stroke risk indicates that the risk is not increased.¹²

Choosing an HT formulation

Consider the pharmacokinetic profile. Many oral estrogen HT products have rapid-release characteristics that make them likely to contribute to rapid rises and falls in the user's estrogen level. Oral estrogens also are associated with procoagulant properties that may increase the risk of thrombosis and thromboembolism. Nonoral estrogens do not appear to increase these risks.¹³

Nonoral estrogens (patches, gels, sprays, lotions, and vaginal rings) provide a more stable pharmacokinetic profile, as do some oral products with controlled-release properties.

FAST TRACK

The elevated risk of stroke associated with use of OCs by women with migraine with aura appears to relate, in particular, to older, higher-dose OC formulations

Do you have a menopause management dilemma?

See page 24

Hormone therapy is one option for postmenopausal migraineurs with bothersome vasomotor symptoms

Many women with a history of migraine move into menopause expecting their condition to improve, says headache expert Anne H. Calhoun, MD, a founder of the Carolina Headache Institute in Chapel Hill, North Carolina.

“Over the years, these women have heard that things get better with menopause.”

For women with a history of episodic migraine, that expectation is realistic, Calhoun says. “But for women with chronic migraine, who may experience a low-grade headache on a daily, or almost daily basis, with 10 or 12 severe headaches in a month, things usually get worse after menopause because the sleep issues of menopause are superimposed on the migraine.”

Dr. Calhoun observes that hormone therapy (HT) has never been contraindicated in women with migraine, although many neurologists are hesitant to prescribe any hormones for this population.

Before prescribing HT to a postmenopausal migraineur, Dr. Calhoun considers a range of variables, including sleep patterns, current medications, anxiety, frequency and severity of vasomotor symptoms, and any other problems the patient may be experiencing.

“It’s basically the same assessment as with any postmenopausal patient—to determine whether HT is a reasonable option,” she says.

And when she determines that HT is appropriate, “I almost exclusively use transdermal HT. I also am more likely to prescribe continuous use of a transdermal patch or skin gel, as I want to achieve very consistent hormone levels, day in and day out,” she says.



For an in-depth interview with headache expert Dr. Anne H. Calhoun on the use of combination OCs in premenopausal migraineurs, visit our online Audio Library at obgmanagement.com. For a glimpse of what you'll find online, see page 50.

As for progestins, some formulations (medroxyprogesterone acetate) tend to cause vasoconstriction, whereas others (micronized progesterone) tend to be vasodilators. Whether these properties affect the rate of migraine or risk of stroke is unclear.

My management approach for this patient

In the absence of any systematic data on the use of HT in this clinical setting, and without any concrete suggestions from migraine experts, I would take the following three-step approach:

1. I would begin with a low-dose nonoral estradiol formulation, prescribing it without a progestin even in a woman who still has a uterus. My aim: to determine the lowest effective dose of HT for this particular patient. I would follow the patient on this dose for 3 months.

DR. PINKERTON Another goal is to determine whether transdermal estradiol increases headaches.

Before settling on a therapy, however, I would ask how long this patient has been postmenopausal, how long she has been experiencing vasomotor symptoms, and how severe those symptoms are. For example, is she having 7 or 8 hot flashes per day and waking from night sweats once or twice per night? I also would ask her how long she remained on the venlafaxine. The additional information would allow me to fine-tune her treatment.

2. If this formulation is tolerated, I would add micronized progesterone (oral or vaginal) for endometrial protection.

DR. PINKERTON I would give oral progesterone if it is FDA approved for postmenopausal use, vaginal progesterone if it isn't.

3. I would follow the patient's clinical response—specifically, her vasomotor symptoms and rate of migraine with or without aura.

My bottom line

No systematic data on the use of HT in migraineurs has been published. In the absence of such data, some practitioners have extrapolated data on the use of OCs in this population and decline to prescribe HT to women with migraine. However, HT and OCs are vastly different in formulation, dose, and risks. Rather than make assumptions on the basis of irrelevant data, we should conduct studies of HT use in migraineurs.

Women who have menstrually related migraine typically have an increased risk of migraine during perimenopause and a significant reduction in migraine following menopause. If hot flashes are bothersome, these women certainly can use HT. I recommend prescribing HT in a continuous fashion that maintains stable hormone levels in the blood, as fluctuating hormones tend to trigger migraines.

CONTINUED ON PAGE 24

DR. KAUNITZ *I would just add that transdermal estradiol is preferred, to be given at the lowest effective dose. ☺*

Disclosures

Dr. Kaunitz reports that his institution receives grant or research support from Bayer, Teva, and Noven, and that he is a consultant to Bayer, Actavis, and Teva.

Dr. Pinkerton reports that her institution receives consulting fees from Pfizer, DepoMed, Shionogi, and Noven and multicenter research fees from DepoMed, EndoCeutics, and Bionova.

Dr. Simon reports that he has served (within the past year) or is serving as a consultant or advisory to Abbott, Agile, Amgen, Apotex, Ascend, BioSante, Depomed, Everett, Intimina, Lupin, Therapeutics MD, Meda, Merck, Novartis, Noven, Novo Nordisk, Novogyne, Pfizer, Shionogi, Shippan Point Advisors LLC, Slate, Sprout, Teva, Warner Chilcott, and Watson. He has received (within the past year) or is receiving grant/research support from Abbott, BioSante, EndoCeutics, Novo Nordisk, Novogyne, Palatin, Teva, and Warner Chilcott. He has served (within the past year) or is serving as a speaker for Amgen, Eisai, Merck, Novartis, Noven, Novo Nordisk, Novogyne, Shionogi, Teva, and Warner Chilcott. Dr. Simon was the Chief Medical Officer for Sprout Pharmaceuticals.

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Do you have a troubling case in menopause?

Suggest it to our expert panel. They may address your management dilemma in a future issue!

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