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# Women's health update: A literature review impacting primary care

## ABSTRACT

The authors review studies on key issues in women's health with potential impact on internal medicine practice. The reviewed articles discuss cardiovascular disease risks, bone health, breast cancer genetics, cervical cancer prevention, depression in the peripartum period, pelvic pain, and emergency contraception.

## INTRODUCTION

THE KEY ISSUES IN WOMEN'S HEALTH continue to be cardiovascular disease risk, bone health, breast cancer risk, cervical cancer prevention, postpartum depression, pelvic pain, and emergency contraception. The authors review studies on these topics with potential impact on internal medicine practice.

This article includes the most significant publications from women's health medical literature between April 1, 2020, and February 28, 2021. The authors independently reviewed and ranked articles in 16 medical journals based on strength of evidence, innovative nature of information, and how evidence will change clinical practice. Articles with strong methodology and practice-changing guidance are included.<sup>1-14</sup>

## CARDIOVASCULAR DISEASE RISK STRATIFICATION: MIGRAINES WITH AURA, MENOPAUSAL VASOMOTOR SYMPTOMS

*A 49-year-old woman has had migraines accompanied by aura for a year and recently developed hot flashes that awaken her from sleep 4 nights each week. Her sister also experiences migraines and was started on a statin as*

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*her doctor noted her increased risk for heart disease. The patient asks if she needs medication to reduce her own risk.*

### Migraines with aura and cardiovascular risk

Migraines with aura have been associated with higher adjusted incidence of cardiovascular disease (CVD) in women but how this risk compares with other risk factors has not been known.<sup>1,15,16</sup>

A study by Kurth and colleagues<sup>1</sup> evaluated the association of migraine with aura and risk of CVD. A total of 27,858 US female health professionals (mean age 54.7), without CVD at baseline, provided lipid measurements. At baseline, 1,435 (5.2%) self-reported a history of migraine with aura, 2,177 reported migraine without aura, and 24,246 had no migraine. The primary outcome was major CVD, including first myocardial infarction, stroke, or CVD death. Participants were followed for a mean 22.6 years.

For women with migraine with aura, the adjusted incidence rate of major CVD events was 3.36 (95% confidence interval [CI] 2.72-3.99) per 1,000 person years compared with 2.11 (95% CI 1.98-2.24) for migraine without aura, a statistically significant difference ( $P < .001$ ).<sup>1</sup> The risk associated with migraine with aura was significantly higher than that associated with obesity, low high-density lipoprotein cholesterol, or high triglycerides but not significantly different than participants with elevated systolic blood pressure, high total cholesterol, or family history of myocardial infarction prior to age 60. The CVD incidence rates associated with current smoking and diabetes was significantly higher than those with migraine with aura ( $P = .02$ ).

An important limitation of this study<sup>1</sup> is that data were self-reported. In addition, information regarding management of migraines and other risk factors was not available. While this paper demonstrates increased risk for cardiovascular events in women

with migraine with aura, to date, evidence is limited with respect to targeted use of aspirin or statins for prevention in this population.

### Menopausal vasomotor symptoms and cardiovascular risk

Prior studies have suggested that vasomotor symptoms (eg, hot flashes, night sweats) are associated with an unfavorable CVD risk profile, but the association with clinical CVD has been less clear.<sup>17-23</sup>

Zhu and colleagues<sup>2</sup> published a pooled analysis of 23,365 women in 6 prospective studies that contributed to the InterLACE (International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events) Consortium. Predictors included frequency, severity, and timing of vasomotor symptoms; the primary outcome was incidence of CVD. Using Cox proportional hazard models, hazard ratios were estimated for the association of vasomotor symptoms with CVD incidence. Vasomotor symptom severity was measured as never, mild, moderate, or severe.

### Consider the possibility that migraine with aura and menopausal vasomotor symptoms can be risk factors for cardiovascular disease

There was no association between the frequency of vasomotor symptoms and CVD.<sup>2</sup> Severe vasomotor symptoms were associated with an increased risk of CVD. The hazard ratio for the association between CVD and hot flashes, night sweats, and any vasomotor symptoms was 1.83 (95% CI 1.22–2.73), 1.59 (95% CI 1.07–2.37), and 2.11 (95% CI 1.62–2.76), respectively. Early or late onset of symptoms were associated with increased CVD incidence when compared with no symptoms. In conclusion, severe vasomotor symptoms, not frequency, are associated with an increased risk for CVD.

### History of migraine with aura or menopausal vasomotor symptoms and risk assessment

Women with migraine with aura had a higher adjusted CVD incidence than women with migraine without aura or women without migraine.<sup>2</sup> The degree of risk was similar to that associated with elevated systolic blood pressure or high total cholesterol. Severity of vasomotor symptoms, but not frequency, may also help with identifying women at higher risk for CVD.

Our approach is to consider migraine with aura and menopausal vasomotor symptoms as risk factors when engaging in shared decision-making with patients to reduce cardiovascular risk.

### ■ BONE HEALTH

*A 73-year-old woman has been taking alendronate for 3 years, however, recently read that alendronate could increase fracture risks. She asked if she should stop or shorten therapy duration.*

#### Atypical femur fractures vs fracture prevention

Bisphosphonates reduce hip fracture risk and are first-line medication for osteoporosis treatment,<sup>24,25</sup> however, have been associated with atypical femoral fractures and osteonecrosis of the jaw.<sup>26</sup> When communicating with patients about bisphosphonate use, discussing the magnitude of benefits and risks fosters shared decision-making.

Black and colleagues<sup>3</sup> evaluated the association between bisphosphonate use and atypical femoral fracture in female patients ages 50 and over who were receiving bisphosphonates between 2007 and 2017 and were enrolled in the Kaiser Permanente Southern California healthcare system. Atypical femoral fracture was the primary outcome, and bisphosphonate-associated atypical fractures were compared with other prevented fractures when bisphosphonate use was terminated.

In 196,129 women who used bisphosphonates at any time during the study period, 277 experienced atypical femoral fractures (1.74 fractures per 10,000 patient years).<sup>3</sup> The incidence of atypical fractures increased as duration of bisphosphonate use increased. The hazard ratio for duration of use (compared with use < 3 months) was 8.86 (95% CI 2.79–28.20) for 3 to 5 years and 43.51 (95% CI 13.70–138.15) for 8 or more years. Race impacted risk (hazard ratio for Asian vs White patients 4.84; 95% CI 3.57–6.56), as did shorter height, higher weight, and glucocorticoid use. Atypical femoral fractures rapidly decreased with bisphosphonate discontinuation,<sup>3</sup> although the absolute risk of atypical femur fracture remained very low compared with reduction in risk of hip, vertebral, and humerus fractures with continuation of bisphosphonate treatment.<sup>4</sup>

In 10,000 White women treated for 3 years, there would be 149 hip fractures prevented and two atypical femoral fracture would occur.<sup>3</sup> In 10,000 Asian women treated for 3 years, 91 hip fractures would be prevented and 8 atypical femoral fracture would occur.

In conclusion, atypical femoral fracture risk

increased with longer duration of bisphosphonate treatment and declined rapidly after discontinuation. The absolute risk of atypical femoral fracture remains low compared to the reduction in hip, vertebral, and humerus fractures with bisphosphonate treatment.

### Optimal duration of bisphosphonate therapy

Although the optimal duration of treatment with bisphosphonates remains uncertain, the 2017 American College of Physicians guidelines recommend treating osteoporotic women with pharmacologic therapy for 5 years and to consider a longer duration of treatment in higher-risk individuals.<sup>27</sup>

Determining the continuation of bisphosphonate treatment after 5 years is complicated. In a recent retrospective study of 29,685 women who had taken bisphosphonates for 5 years, authors evaluated the impact of stopping therapy, continuing for 2 years, or continuing for 5 more years on hip fracture incidence.<sup>5</sup> There was no difference in hip fracture incidence for patients who continued for 5 more years, compared with patients who stopped after 5 years. However, hip fracture risk was lower in those who continued for only 2 additional years and then stopped. Discontinuation of bisphosphonates at different time intervals needs additional study.

### Should this patient continue bisphosphonate therapy?

Although atypical femoral fractures are associated with bisphosphonate use, the absolute risk remains low compared with the reduction in hip and other fractures. Our patient should continue bisphosphonate treatment and should complete at least 5 years of treatment. Decision-making about continuing treatment beyond 5 years remains complicated and should be evaluated at that time.

## ■ PERIPARTUM DEPRESSION MANAGEMENT AND DIAGNOSIS

*A 34-year-old woman, pregnant for the first time and in her first trimester, indicated that she is having increasing symptoms of both anxiety and depression. The Edinburgh Postnatal Depression Scale was administered resulting in a score of 11. During the visit, the patient wonders if she should continue to take duloxetine, prescribed for her diagnosis of relapsing-remitting depression, during pregnancy.*

Depression in pregnancy is common,<sup>28</sup> is often undertreated,<sup>29</sup> and has been associated with adverse outcomes for the mother, developing fetus, and newborn.<sup>30,31</sup> The 10-item Edinburgh Postnatal Depression Scale is universally accepted, used,

and recommended by the US Preventive Services Task Force.<sup>32,33</sup> However, the US Preventive Services Task Force does not specify a cutoff value for depression diagnosis in pregnant and postpartum patients.<sup>33,34</sup>

### Depression screening during pregnancy and postpartum

The Edinburgh Postnatal Depression Scale screening accuracy in pregnant and postpartum women was evaluated in a systematic review and meta-analysis of individual participant data from 58 studies (15,557 women at least 18 years of age, 2,069 with major depression).<sup>6</sup> Data included both Edinburgh Postnatal Depression Scale scores and major depression classification based on validated interviews. Assessments were conducted no more than 2 weeks apart, either during pregnancy or within 12 months of giving birth.

Overall, combined sensitivity and specificity for depression diagnosis were maximized at a cutoff value of  $\geq 11$  (81% and 88%, respectively).<sup>6</sup> Accuracy was similar in pregnant and postpartum women. A cutoff value of  $\geq 13$  was less sensitive but more specific (66% and 95%, respectively) and may be more useful in identifying women with a high symptom burden.

### Is duloxetine safe in pregnancy?

Duloxetine is a selective serotonin-norepinephrine reuptake inhibitor used in the treatment of depression, fibromyalgia, chronic musculoskeletal pain, and generalized anxiety disorder—all conditions that commonly affect women of childbearing age.<sup>35</sup> Limited safety data exist with respect to adverse pregnancy outcomes.

Huybrechts et al<sup>7</sup> conducted a population-based cohort study using data from the United States Medicaid Analytic eXtract from 2004 to 2013 to evaluate the risk of adverse maternal and infant outcomes following in utero exposure to duloxetine.

The study population included pregnant women ages 18 to 55 and their live-born infants who were exposed to duloxetine.<sup>7</sup> Exposure was defined as filling at least 1 outpatient prescription for duloxetine. Authors considered 4 reference groups:

- Women not exposed to duloxetine
- Women exposed to selective serotonin reuptake inhibitors
- Women exposed to another serotonin-norepinephrine reuptake inhibitor (venlafaxine)
- Women exposed to duloxetine before but not during pregnancy.

Primary outcomes included congenital malformations, preterm birth, cardiac malformations,

small for gestational age infant, pre-eclampsia, and postpartum hemorrhage.<sup>7</sup> Several potential confounding variables were considered, and propensity score stratification was used to account for imbalances between groups.

Compared with unexposed pregnancies, there was no increased risk of congenital malformations overall, preterm birth, or pre-eclampsia.<sup>7</sup> Results indicate significantly increased risk for postpartum hemorrhage with duloxetine exposure only in late pregnancy (adjusted relative risk [RR] 1.53, 95% CI 1.08–2.18) when compared with unexposed women and those with selective serotonin reuptake inhibitor exposure. The increased risk of postpartum hemorrhage was also present for venlafaxine-exposed women, suggesting a class effect. When compared with unexposed pregnancies, results demonstrated a small *potential* increased risk in duloxetine-exposed pregnancies for cardiovascular anomalies (adjusted RR 1.29, 95% CI 0.99–1.68) and small-for-gestation-age infants (early pregnancy exposure: adjusted RR 1.14, 95% CI 0.92–1.41; late pregnancy exposure: adjusted RR 1.20, 95% CI 0.83–1.72). Notably, these findings were not statistically significant and were not demonstrated within other groups.

**Does this patient have a positive screening test for depression? Should she continue duloxetine during pregnancy?**

This patient screened positive for depression. Additionally, duloxetine does not appear to be a teratogen. This visit provides an opportunity to counsel the patient regarding treatment options during pregnancy and to explore adjunctive pharmacologic and non-pharmacologic options and risks.<sup>36–38</sup> Potential small increased risks of relatively uncommon outcomes must be weighed against the benefits of treating depression and pain during pregnancy, for the health of both mother and infant. This should be a shared, individualized decision. In this patient, with increasing symptoms of anxiety and depression early in pregnancy, it would be reasonable to continue duloxetine with adjunctive interpersonal therapy or cognitive behavioral therapy, or both.<sup>38</sup>

**■ BREAST CANCER RISK GENES**

*A 56-year-old woman with a strong family history of estrogen receptor-negative/progesterone receptor-negative/human epidermal growth factor receptor-2 breast cancer had tested negative for mutation of the BRCA1 and BRCA 2 genes 15 years ago. Recently, her sister had been*

*diagnosed with breast cancer despite prior negative testing, and she wondered what, if anything, she should do.*

**Breast cancer genetics**

Between 5% to 10% of patients with breast cancer have a pathologic genetic variant, thus the US Preventive Services Task Force recommends that women with a personal or family history of breast or ovarian cancer be screened with one of several breast cancer risk assessment tools and offered genetic counseling and possibly genetic testing based on the results.<sup>39</sup> Since the identification of *BRCA1* and *BRCA2* in the mid-1990s, genetic testing for cancer susceptibility has become more affordable and more common. Several multigene panel tests are available for clinician use.<sup>40</sup> These panels include breast cancer risk genes as well as variants of uncertain significance, leading to challenges in interpretation.<sup>40</sup>

**Genes most associated with breast cancer**

Two studies addressed genetic variants and breast cancer risk.<sup>8,9</sup> Hu et al<sup>8</sup> and the Breast Cancer Association Consortium<sup>9</sup> published population-based case-control studies with similar results. Hu et al compared 32,247 US breast cancer patients with 32,544 healthy controls by sending the same multigene panel with 28 cancer-predisposition genes from both groups.<sup>8</sup> Most participants in the sample (75%) identified as White.<sup>8</sup> The Breast Cancer Association Consortium study included 60,466 breast cancer patients and 53,461 controls from 27 mostly European countries and used a similar panel with 34 putative susceptibility genes in their analysis.<sup>9</sup> In both studies, the multigene panel analysis was applied to previously collected DNA samples that were entered into consortium databases with patient consent.<sup>8,9</sup>

Several genes were found to be significantly associated with strong or moderate breast cancer risk: *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, and *ATM*.<sup>8,9,41,42</sup> *BRCA1*, *BRCA2*, and *PALB2* conferred the highest breast cancer risk, aligning with current guidelines to discuss risk-reducing mastectomy with those patients.<sup>41,42</sup> *CHEK2* and *ATM* were associated with elevated, but more moderate, risk. In the study by Hu et al,<sup>8</sup> *BRCA1*, *BRCA2*, and *PALB2* conferred the strongest risk for breast cancer, with odds ratios ranging from 3.83 for *PALB2* (95% CI 2.68–5.63, *P* < .001) to 7.62 for *BRCA1* (95% CI 5.33–11.27, *P* < .001). More moderate risk for breast cancer was associated with *CHEK2* (odds ratio 2.47, 95% CI 2.02–3.05, *P* < .001) and *ATM* (odds ratio 1.82, 95% CI 1.46–2.27, *P* < .001) genes. Notably, in both stud-



ies, the majority of variants of uncertain significance were not associated with breast cancer risk.<sup>8,9</sup>

### Does this patient need to be re-tested for breast cancer risk genes?

Additional genes have been identified since this patient's test 15 years ago. While ideally, the person who experienced breast cancer (in this case, the patient's sister) would be re-tested, this is not always possible for a given patient. The patient's family history meets guidelines for genetic testing, and it is reasonable to offer repeat testing to look for these additional culprit genes.<sup>8,9</sup> Additionally, she may be a candidate for chemoprevention or breast magnetic resonance imaging<sup>43</sup> depending on results of individualized risk assessment, regardless of the genetic testing outcome.

## ■ CERVICAL CANCER PREVENTION

*A 41-year-old patient returned to your office after seeing her obstetrician-gynecologist for management of cervical intraepithelial neoplasia (CIN) 2. She asked if there is anything to do to reduce her cervical cancer risk. She shared that she had been uncertain about vaccinating her 11-year-old daughter but was now reconsidering, asking, "Does this vaccine really prevent cervical cancer?"*

### Human papillomavirus virus vaccination indications

The US Food and Drug Administration approved a quadrivalent human papillomavirus (HPV) vaccine in 2006 while the currently used 9-valent version was subsequently approved and prevents infection with 7 cancer-associated HPV types (16, 18, 31, 33, 45, 52, 58) and 2 genital wart-associated HPV types (6, 11).<sup>44</sup> Individuals ages 9 through 45 may be vaccinated, though the Advisory Committee on Immunization Practices recommends routine vaccination only for persons ages 9 through 26 and shared decision-making for catch-up vaccination in adults ages 27 to 45.<sup>45</sup> In 2018, only 51% of US adolescents were up-to-date with the HPV vaccine series.<sup>46</sup>

## HPV vaccination has now been demonstrated to reduce the risk of cancer, as well as invasive CIN

### HPV vaccine as adjuvant therapy for high-grade cervical intraepithelial neoplasia

Receipt of the quadrivalent HPV vaccine may reduce the risk of recurrent, high-grade CIN when used as adjuvant therapy for cervical dysplasia.<sup>47,48</sup> Lichter et al<sup>10</sup> performed a systematic review and meta-analysis

to evaluate the efficacy of adjuvant HPV vaccination in preventing recurrence after surgical excision by studying 2,984 women in 6 studies who had received a diagnosis of CIN 2 or greater. Patients with invasive disease, immunodeficiency, or autoimmune conditions were excluded. All patients underwent surgical excision, and only the intervention group members also received adjuvant HPV vaccination. Comparison group members received placebo or surgical management alone. At 6 to 48 months, recurrence of CIN 2 or greater was significantly decreased in HPV vaccine recipients (RR 0.36, 95% CI 0.23–0.55) with a number needed to treat for benefit (NNTb) of 28. Recurrence of CIN 1 or greater irrespective of HPV type was decreased (RR 0.67, 95% CI 0.52–0.85; NNTb 30), and recurrence of CIN 2 or greater with HPV 16 or 18 was also decreased (RR 0.41, 95% CI 0.20–0.85, NNTb 83).

### HPV vaccination for primary prevention of cervical cancer

Previous studies of HPV vaccination used the surrogate endpoint of prevention of high-grade cervical cancer lesions to evaluate efficacy. In this registry-based cohort study, Lei et al<sup>11</sup> evaluated the rate of invasive cervical cancer in 1,672,983 Swedish girls and women ages 10 to 30 from 2006 to 2017 received either  $\geq 1$  dose of the quadrivalent HPV vaccination or no HPV immunization. After adjustment for covariates, cervical cancer incidence was reduced in the intervention group by 88% if the immunization occurred prior to age 17, as demonstrated by an incidence rate ratio of cervical cancer of 0.12 (95% CI 0.00–0.34); for those immunized between ages 17 and 30, cervical cancer incidence was reduced by 53%, with an adjusted incidence rate ratio of 0.38 (95% CI 0.12–0.72).

### Should this patient and her daughter receive HPV vaccination?

Given the safety of HPV vaccination and relatively low NNTb, this patient should receive HPV vaccination. As her daughter is under 17, now is the ideal time for cervical cancer prevention with HPV immunization.

## ■ EMERGENCY CONTRACEPTION

*A 31-year-old woman participated in unprotected intercourse 2 days before presenting at the clinic. She tried to obtain ulipristal from the pharmacy, but it was not in stock. She heard that intrauterine devices (IUDs) are effective emergency contraception and asked for "the one that leads to lighter periods."*

### Levonorgestrel IUD as emergency contraception

Observational studies have suggested that levonorgestrel IUDs may be effective for emergency contraception. Turok et al<sup>12</sup> performed a randomized, controlled trial comparing levonorgestrel and copper IUDs for emergency contraception. Inclusion criteria included women ages 18 to 35, fluent in English or Spanish, requesting emergency contraception after unprotected sexual intercourse within the previous 5 days (120 hours). Other eligibility involved participants with a desire to initiate use of an IUD, to prevent pregnancy for at least 1 year, negative urine pregnancy test, history of regular menstrual cycles, and known date of last menstrual period. Women were excluded if they were breast feeding, had vaginal bleeding of unknown origin, intrauterine infection within 3 months, untreated gonorrheal or chlamydia infection within prior 30 days, used oral emergency contraception within the preceding 5 days, or had copper allergy.

The intervention cohort received IUD (levonorgestrel 52 mg), and the control group received copper IUDs.<sup>12</sup> The primary outcome was a positive urine pregnancy test 1 month after IUD insertion using a noninferiority margin of 2.5 percentage points; secondary outcomes included IUD discontinuation, participant satisfaction, and bleeding outcomes.

Over one-quarter of patients had a body mass index > 30 kg/m<sup>2</sup>; 711 women presented to 6 different sites in Utah seeking emergency contraception.<sup>12</sup> For the primary outcome of pregnancy, there was 1 pregnancy in 317 participants who received the levonorgestrel IUD and 0 pregnancies in 321 participants who received the copper IUD—the between-group absolute incidence was 0.3, which was not statistically significant. There was no difference between groups in rates of IUD expulsion, removal, or need for medical care within 1 month of IUD placement. Satisfaction rates were similar.

### Can this patient be offered a 52-mg levonorgestrel IUD for emergency contraception?

This study demonstrates that levonorgestrel 52-mg IUD is noninferior to the copper IUD in providing emergency contraception.<sup>12</sup> As this patient reports an interest in lighter menses, the levonorgestrel IUD may be an appropriate therapeutic option to offer in shared decision-making, particularly when body mass index limits the effectiveness of other emergency contraception options. However, the US Food and Drug Administration has not yet approved levonorgestrel IUD for emergency contraception, which may limit its use for this indication.

### CURRENT TREATMENT OF CHRONIC PELVIC PAIN

*A female patient presented for follow-up of chronic pelvic pain. She previously underwent extensive evaluation, including laparoscopy, which did not reveal the cause of her symptoms. Her aunt takes gabapentin for chronic pain, and she asks if this is a good treatment option for her.*

Chronic pelvic pain refers to noncyclic pain localized to the pelvis, lasting 3 to 6 months, and is associated with substantially reduced quality of life for affected individuals.<sup>49</sup> While comprehensive history taking, physical examination, and testing may identify a specific etiology, often, the etiology is complex involving pelvic floor disorders, may overlap with other chronic pain syndromes such as irritable bowel syndrome or bladder pain syndrome, or may not have an identifiable cause.<sup>13</sup> Many individuals who have experienced trauma suffer from chronic pelvic pain.<sup>13,49</sup>

### Gabapentin for chronic pelvic pain

Current pathophysiologic models focus on a common pathway involving the central pain response,<sup>13</sup> and gabapentin is often chosen as treatment based on its efficacy in other chronic pain conditions.<sup>50</sup> Small trials have shown modest improvement in pain for patients with chronic pelvic pain treated with gabapentin.<sup>51,52</sup>

Horne et al<sup>14</sup> performed a larger multicenter, randomized, double-blind, placebo-controlled trial in 39 hospital centers in the United Kingdom to assess the efficacy and safety of gabapentin for the treatment of chronic pelvic pain in women with no structural or infectious cause of symptoms. Participants were included (n = 306) if they had experienced chronic pelvic pain for at least 3 months with or without dysmenorrhea, were using contraception, and had no evidence of pelvic pathology on laparoscopy performed at least 2 weeks and less than 36 months before enrollment. Similar to previous trials, intervention group participants received gabapentin, titrated to a maximum dose of 2,700 mg/day; control group participants received matching placebo. The primary outcome was a reduction in pain on a rating scale (0–10) and reported adverse events at 16 weeks.

At baseline, the majority of participants experienced dysmenorrhea, were using hormonal contraception, identified as White, and had previously used non-steroidal anti-inflammatory drugs and opiates as rescue medications.<sup>14</sup> Baseline pain scores between groups were similar, with average scores of 5.5 in both groups and worst scores of 8.4 and 8.6 in treatment

and placebo groups on a 10-point scale.

At 16 weeks, there was no difference between groups in either worst pain score or average pain scores.<sup>14</sup> Participants in the gabapentin cohort had a mean decrease in average pain scores of 1.1 (standard deviation [SD] 2.0) and decrease in worst pain scores of 1.4 (SD 2.3); the placebo cohort reported decreases of 0.9 (SD 1.8) in average pain score and 1.2 (SD 2.1) in worst pain score. Significantly more participants in the gabapentin cohort reported adverse events that included dizziness (54% vs. 28%, risk ratio 1.91,  $P = .0002$ ), drowsiness (52% vs 29%, risk ratio 1.71,  $P = .002$ ), and visual disturbances (22% vs 11%, risk ratio 2.25,  $P = .01$ ).<sup>14</sup>

Strengths of the trial include its size; prior trials included fewer than 100 patients each.<sup>14</sup> The trial ended after 16 weeks, which may have limited its ability to detect a difference with longer-term use as seen in the smaller studies. However, none of the gabapentin trials offer insight into participants' comorbid pain conditions or participation in multidisciplinary treatment approaches, a limitation in their generalizability.<sup>14,51,52</sup>

### Should this patient be offered gabapentin?

In Horne et al,<sup>14</sup> gabapentin did not result in lower pain scores but led to more dizziness, drowsiness, and visual disturbances than placebo, and earlier, smaller studies showed modest benefit.<sup>14,51,52</sup> Clinicians considering the use of gabapentin to treat chronic pelvic pain should note the side effects and potential modest effects when discussing with patients and determining next steps in shared decision-making.

### TAKE-HOME POINTS

- Migraine with aura and severe vasomotor menopausal symptoms can be considered when determining a patient's cardiovascular disease risk.
- Consider overall benefits and risks of bisphosphonates when counseling patients, specifically the low incidence of atypical femoral fracture compared with reduction in hip fractures.
- Obtain breast cancer genetics evaluation in patients meeting National Comprehensive Cancer Network criteria who have either never had genetic testing or did not have testing for *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, and *ATM* genes.
- Compared with unexposed pregnancies, duloxetine exposure confers no increased risk of congenital malformations, preterm birth, or pre-eclampsia. There is a small increase in risk for postpartum hemorrhage with late-pregnancy exposure (adjusted

relative risk 1.53, 95% CI 1.08–2.18).<sup>7</sup> Duloxetine is unlikely to be a major teratogen.

- The Edinburgh Pregnancy Depression Scale can be used to diagnose depression in pregnant and postpartum patients.
- HPV vaccination for primary prevention of cervical cancer can be considered as adjuvant therapy for women being treated for CIN 2 or greater.
- The levonorgestrel intrauterine device appears to be noninferior to the copper intrauterine device for emergency contraception; however, it is not yet approved for this indication by the United States Food and Drug Administration.
- Current evidence suggests caution when using gabapentin to treat chronic pelvic pain in women, with shared decision-making to discuss potential side effects and expected benefit. ■

### DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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