The effectiveness and value of fezolinetant for moderate-to-severe vasomotor symptoms associated with menopause: A summary from the Institute for Clinical and Economic Review's Midwest Public Advisory Council

Abigail C Wright, PhD, MSc; Francesca L Beaudoin, MD, PhD, MS; R. Brett McQueen, PhD; Kai Yeung, PharmD, PhD; Ashton Moradi, Pharm D, MS; Serina Herron-Smith, BA; Eric Gutierrez, MPH; Grace A Lin, MD; Steven D Pearson, MD, MSc

Background

Of women undergoing menopause, approximately 80% experience vasomotor symptoms (VMS), also known as hot flashes. Hot flashes are thought to be due to changes in hormones involved in body temperature regulation, such as estrogen and neurokinin B.[1-3] Moderate VMS (heat with sweating) and severe VMS (heat with sweating causing cessation of activities) occur in one-third to half of women, frequently interfering with sleep, concentration, mood, energy, and sexual activity.[4] VMS are estimated to increase direct health care costs by $1,300 per person per year and increase indirect economic costs due to missed work by another $770 per person per year.[5] For women with moderate-to-severe VMS and no medical contraindications, menopausal hormone therapy (MHT), consisting of estrogen with or without progesterone, is recommended as first-line therapy.[6] In women who have contraindications to MHT, nonhormonal treatments (eg, antidepressants and gabapentinoids) may be considered.

Fezolinetant (Astellas Pharma Inc.) is a once-daily oral nonhormonal therapy being investigated for the treatment of moderate-to-severe VMS associated with menopause. It acts by regulating the neurokinin-3 receptor in the hypothalamus, thereby affecting temperature regulation. If approved, it would be the first selective neurokinin-3 receptor antagonist available in the United States. Astellas has submitted a New Drug Application for fezolinetant 45 mg to the US Food and Drug Administration.[7,8] At the time of this publication, a regulatory decision was still pending.

The Institute for Clinical and Economic Review (ICER) conducted a systematic literature review and cost-effectiveness analysis to evaluate the health and economic outcomes of fezolinetant, MHT, antidepressants (selective serotonin reuptake inhibitors [SSRIs]/serotonin norepinephrine reuptake inhibitors [SNRIs]), and gabapentinoids (gabapentin and pregabalin) in women with moderate-to-severe VMS associated with menopause. We present the summary of our findings and highlights of the policy discussion with key stakeholders held at a public meeting of the Midwest Comparative Effectiveness Public Advisory Council (CEPAC) on December 16, 2022. The detailed report is available on ICER's website at https://icer.org/assessment/vasomotor-symptoms-menopause-2022/.

Author affiliations

Institute for Clinical and Economic Review, Boston, MA (Wright, Beaudoin, Moradi, Herron-Smith, Lin, Pearson); Department of Epidemiology, Brown University, Providence, RI (Beaudoin); School of Pharmacy, University of Colorado, Aurora (McQueen and Gutierrez); Kaiser Permanente Washington Health Research Institute, Seattle (Yeung).

AUTHOR CORRESPONDENCE:
Abigail C Wright, 1.617.528.4013; awright@icer.org

J Manag Care Spec Pharm. 2023;29(6):692-98

Copyright©2023, Academy of Managed Care Pharmacy. All rights reserved.

Summary of Findings

Below we review studies for fezolinetant, MHT, SSRIs/SNRIs, and gabapentin that met our inclusion criteria. There were no studies of pregabalin that met our inclusion criteria. For key results across all trials, see Table 3.2 in the ICER report found at https://icer.org/wp-content/uploads/2022/06/ICER_Menopause_FinalReport_01232023.pdf. A network meta-analysis was not

performed because of significant heterogeneity in the assessment of study endpoints (eg, VMS and quality of life).

FEZOLINETANT

The pivotal trials of fezolinetant 45 mg are two 12-week randomized controlled trials (RCTs) with an extension phase lasting an additional 40 weeks (Skylight 1 and Skylight 2).[9-11] The evidence base also includes two 52-week trials examining safety and tolerability (Skylight 4 and Moonlight 3).[12-14] An additional RCT examined the efficacy of a lower 30 mg dose only in an Asian population (Moonlight 1). Participants in all fezolinetant trials were women aged 40-65 years who had a body mass index no higher than 38kg/m^2 with a minimum average of 7-8 moderate-to-severe hot flashes per day or 50-60 per week.

In the Skylight 1 and 2 trials, participants in the fezolinetant group had a significantly greater reduction in VMS frequency at 12 weeks,[9,15,16] although the difference did not meet the minimum clinically important difference (MCID) defined in the literature (>3.57 hot flashes daily).[17] Participants treated with fezolinetant also had a significantly greater reduction in VMS severity at 12 weeks, exceeding the MCID for reduction in severity (>0.225 hot flashes daily)[18] in the Skylight 2 trial, but not in Skylight 1.[9,15,16] Pooled data from the Skylight trials reported that fezolinetant significantly improved scores on the Menopause Quality of Life Questionnaire (MENQoL) compared with placebo,[14] but the difference did not meet the MCID (improvement >1 on any MENQoL domain).[19]

Fezolinetant was generally well tolerated, with headache as the most common adverse event, and with 2%-3% experiencing elevated liver enzymes. Elevations in liver enzymes were generally asymptomatic and resolved after cessation of the study intervention; there were no cases of drug-induced hepatocellular injury with jaundice.[13] The safety trials reported no additional concerns.[12-14]

MHT

Ten RCTs in postmenopausal women evaluated the efficacy of combined estrogen and progesterone or estrogen only in postmenopausal women (either a standard dose [1 mg] or low dose [0.5 mg]) for the treatment of VMS.[20-28] Overall, trials reported significantly greater reductions in VMS frequency and severity and significant improvements in MENQoL in the MHT group compared with the placebo group,[20-31] with the majority meeting the MCID. Short-term adverse events were mostly mild to moderate in severity. There are additional benefits and harms to consider with long-term use. For women age 50-59 years, who represent the majority of women making menopause treatment decisions, significant hazard ratios were greater than 1 for breast cancer ($P>0.05$), stroke ($P>0.05$), and pulmonary embolism ($P<0.05$) and were less than 1 for colorectal cancer ($P<0.05$), hip fracture ($P<0.05$), death ($P>0.05$), and coronary heart disease ($P>0.05$).[32,33]

SSRIs/SNRIs

The efficacy of SSRIs/SNRIs for the treatment of VMS has been evaluated in 10 RCTs.[25,34-41] The results were inconsistent across trials. Although some trials reported statistically significant improvements in VMS, with desvenlafaxine appearing to have the most consistent treatment effect (however, these trials included mild VMS in their assessment of VMS frequency and severity), none of the antidepressants reviewed achieved the MCID in VMS frequency or MENQoL when compared with the placebo group. Adverse events in the SSRI and venlafaxine trials were mostly mild or moderate in severity, with the most common events being fatigue, dry mouth, nausea, and decreased appetite.[25,34-36] Desvenlafaxine trials reported more adverse events in the treatment group than the placebo group, and differences in discontinuation were more apparent at higher doses.[37,38]

GABAPENTIN

The efficacy of gabapentin for the treatment of VMS has been evaluated in 3 RCTs.[42-44] Although demonstrating statistical significance, all trials failed to show clinically meaningful differences in VMS frequency or severity. The MENQoL was not assessed in any of the trials. There were more adverse events in the gabapentin groups compared with the placebo groups, but these were mostly mild to moderate, with the most common events being dizziness, headache, and somnolence.[42,44]

Limitations of the Clinical Evidence

Although the Skylight 1 and 2 trials reported statistically significant improvements in VMS frequency and severity with fezolinetant, the improvement in VMS frequency did not meet the MCID, nor did improvements in MENQoL reach the MCID. Only 1 of the Skylight trials met the MCID for improvement in VMS severity. Adding to our uncertainty about the relative benefits of treatment with fezolinetant is a lack of published data (particularly Moonlight 1, which was a negative trial, albeit at a 30 mg dose) and a lack of evidence on long-term efficacy and safety. As the median total duration of moderate-to-severe VMS among women in the United States is 9.4 years and this is a first-in-class medication for which we cannot rely on safety data from medications in the same therapeutic class, more long-term data for fezolinetant are needed.

Long-Term Cost-Effectiveness

We developed a de novo decision analytic model to evaluate fezolinetant for the treatment of VMS compared with no pharmacologic treatment. We performed separate analyses looking at outcomes and costs within the health care sector and inclusive of broader societal effects, including productivity. The health outcome of each intervention was evaluated in terms of symptom improvements (eg, using the MENQoL), life-years gained, equal value of life-years (evLYs) gained, and quality-adjusted life-years (QALYs) gained. Outcomes were estimated over a lifetime time horizon to capture short-term and ongoing morbidity and mortality. Costs and outcomes were discounted at 3% per year.

The model was focused on an intention-to-treat analysis with a hypothetical cohort of women with VMS being treated with fezolinetant. The first model cycle included treatment costs for all patients until discontinuation, which was based on the typical duration of VMS.[45] Health state occupancy (on treatment, off treatment, or dead) was derived using survival extrapolation methods of the proportion of women with and without VMS during the menopause transition using Kaplan-Meier curves. Full details on ICER's cost-effectiveness analysis and model are available at https://icer.org/news-insights/press-releases/icer-publishes-final-evidence-report-on-fezolinetant-for-vasomotor-symptoms-associated-with-menopause/.

Results of the base case analysis of fezolinetant vs no pharmacologic treatment are shown in Table 1. Fezolinetant incurred additional costs but resulted in more evLYs and QALYs, which were the same given that treatment does not extend life. Incremental cost-effectiveness ratios were $390,000 per evLY or QALY gained and $360,000 per QALY or evLY gained from the modified societal perspective. At an estimated placeholder price of $6,000 annually, fezolinetant exceeds commonly accepted cost-effectiveness thresholds. The annual price range for the drug to meet cost-effectiveness benchmarks of $100,000 to $150,000 per added evLY or QALY gained is $2,000 to $2,600.

TABLE 1 Incremental Cost-Effectiveness Ratios for the Base Case

Intervention	Comparator	Cost per evLY gained[a]	Cost per QALY gained[a]	Cost per symptom-free day[b]
Fezolinetant[a]	No pharmacologic treatment	$390,000	$390,000	$500

[a]*Based on an annual placeholder price of $6,000; interpret findings with caution.*

[b]*The difference in vasomotor symptom episodes on average per cycle (annual) was compared between fezolinetant and placebo and then divided by the average number of vasomotor symptom episodes per day to estimate the total number of symptom-free days.*

evLY = equal value life-year; QALY = quality-adjusted life-year.

Limitations of the Cost-Effectiveness Model

The price of fezolinetant is currently a placeholder price based on market projections for similar drugs, and thus cost-effectiveness estimates must be interpreted with caution. Because of inconsistency in the trial endpoints, we were unable to compare the cost-effectiveness of fezolinetant vs other comparators (eg, MHT). Health-related quality of life was derived using a mapping algorithm between the MENQoL (total score) and the EuroQol-5D. The changes in utility scores are a function of the total changes in MENQoL to allow for health-related quality of life to be associated with VMS and other symptoms correlated with VMS.[46]

Policy Discussion

The Midwest CEPAC is one of the independent appraisal committees convened by ICER to engage in the public deliberation of the evidence on clinical and cost-effectiveness of health care interventions. The CEPAC is composed of medical evidence experts, including clinicians, methodologists, and patient advocates. The ICER report on fezolinetant for moderate-to-severe VMS associated with menopause was the subject of a CEPAC meeting on December 16, 2022. Following the discussion, CEPAC panel members deliberated on key questions raised by ICER's report.

A majority of the panel (11 to 1) voted that the current evidence is inadequate to demonstrate that the net health benefit of fezolinetant for VMS is superior to that provided by no pharmacologic treatment. The panel voted unanimously that the currently available evidence was inadequate to distinguish the net health benefit between fezolinetant and MHT for VMS (Table 2).

The Midwest CEPAC also voted on important "potential other benefits" and "contextual considerations" (Tables 3 and 4) that should be considered by policymakers as they make judgments regarding the value of fezolinetant. No vote was taken for long-term value for money, as a firm estimate of the launch price was not provided by the manufacturer.

Following the discussion of the evidence, a policy roundtable was convened to deliberate on how best to apply the evidence on fezolinetant to treatment for VMS associated with menopause. The full set of policy recommendations can be found in the Final Evidence Report (https://icer.org/news-insights/press-releases/

TABLE 2 Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
Is the currently available evidence adequate to demonstrate that the net health benefit of fezolinetant is superior to that provided by no pharmacologic treatment (neither prescription nor nonprescription) for vasomotor symptoms associated with menopause?	1	11
Is the currently available evidence adequate to distinguish the net health benefit between fezolinetant and menopausal hormone therapy for vasomotor symptoms associated with menopause? If majority yes: Is the currently available evidence adequate to demonstrate that the net health benefit of fezolinetant is superior to that provided by menopausal hormone therapy for vasomotor symptoms associated with menopause?	0	12

TABLE 3 Votes on Other Contextual Considerations (Any Effective Treatment for Vasomotor Symptoms Associated With Menopause)

Contextual consideration	Very low priority	Low priority	Average priority	High priority	Very high priority
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	6	4	2	0	0
Magnitude of the lifetime impact on individual patients of the condition being treated	0	2	2	7	1

TABLE 4 Votes on Other Contextual Considerations (Fezolinetant vs No Pharmacologic Treatment [Neither Prescription nor Nonprescription])

Contextual consideration	Very low priority	Low priority	Average priority	High priority	Very high priority
Patients' ability to achieve major life goals related to education, work, or family life	0	1	7	4	0
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	11	1	0
Society's goal of reducing health inequities	0	1	6	5	0

icer-publishes-final-evidence-report-on-fezolinetant-for-vasomotor-symptoms-associated-with-menopause/). Select key policy recommendations relevant to the potential introduction of fezolinetant into practice are as follows:

1. All stakeholders have a responsibility and an important role to play in ensuring that women have access to effective new treatment options and that new treatments are introduced in a way that encourages shared medical decision making and equitable access.
2. Given the uncertainty in long-term outcomes and the fact that this is a first-in-class therapeutic, it is not unreasonable for payers to consider whether to use the specific trial eligibility criteria to define a threshold for the frequency/severity of VMS that merits coverage. However, clinical experts did not believe that it was appropriate to use strict thresholds based on the frequency of VMS given that patients may have fewer very severe episodes that still have a substantial impact on quality of life.
3. Given that many patients may benefit from readily available, effective, and low-cost MHT, clinical experts agreed that it would be reasonable for payers to require prescriber attestation that patients are not appropriate candidates for MHT prior to prescribing fezolinetant.
4. Manufacturers should set prices that will foster affordability and access for all patients by aligning prices with the therapeutic value, moderated by the substantial uncertainty about longer-term safety and effectiveness.

ACKNOWLEDGMENTS

The authors thank Kelsey Gosselin, Yasmine Kayali, Shahariar Mohammed Fahim, and David Rind for their contributions to this report.

REFERENCES

1. Rance NE, Dacks PA, Mittelman-Smith MA, Romanovsky AA, Krajewski-Hall SJ. Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons: a novel hypothesis on the mechanism of hot flushes. *Front Neuroendocrinol*. 2013;34(3):211-27. doi:10.1016/j.yfrne.2013.07.003

2. Jayasena CN, Comninos AN, Stefanopoulou E, et al. Neurokinin B administration induces hot flushes in women. *Sci Rep*. 2015;5(1):8466. doi:10.1038/srep08466

3. Skorupskaite K, George JT, Veldhuis JD, Millar RP, Anderson RA. Neurokinin 3 receptor antagonism reveals roles for neurokinin B in the regulation of gonadotropin secretion and hot flashes in postmenopausal women. *Neuroendocrinology*. 2018;106(2):148-57. doi:10.1159/000473893

4. Williams RE, Levine KB, Kalilani L, Lewis J, Clark RV. Menopause-specific questionnaire assessment in US population-based study shows negative impact on health-related quality of life. *Maturitas*. 2009;62(2):153-9. doi:10.1016/j.maturitas.2008.12.006

5. Sarrel P, Portman D, Lefebvre P, et al. Incremental direct and indirect costs of untreated vasomotor symptoms. *Menopause*. 2015;22(3):260-6. doi:10.1097/GME.0000000000000320

6. "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-94. doi:10.1097/GME.0000000000002028

7. Astellas Submits Fezolinetant New Drug Application to U.S. FDA [press release]. June 23rd, 2022 2022. Accessed June 24, 2022. https://www.astellas.com/en/news/25931

8. Newswire P. U.S. FDA Accepts Astellas' New Drug Application for Fezolinetant. August 18th, 2022. Accessed August 19, 2022. https://www.prnewswire.com/news-releases/us-fda-accepts-astellas-new-drug-application-for-fezolinetant-301608116.html

9. Johnson KA, Lademacher C, Nappi RE, et al. A Phase 3, randomized, placebo-controlled, 12-week, double-blind study, plus a non-controlled extension treatment period, to assess efficacy and safety of fezolinetant, a neurokinin-3 receptor antagonist, in women with moderate-to-severe vasomotor symptoms associated with menopause. Paper presented at: North American Menopause Society (NAMS) Annual Meeting 2021; September 22–25, 2021; Washington, DC.

10. Johnson KA, Nappi RE, Neal-Perry G, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause: results from a 52-week study (SKYLIGHT 2). Paper presented at: ENDO 2022; June 11–14, 2022; Atlanta, GA.

11. Lederman S, Ottery FD, Cano A, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. *Lancet*. 2023. doi:10.1016/S0140-6736(23)00085-5

12. Astellas. Astellas announces topline results from phase 3 long-term safety study of fezolinetant in mainland China. Published September 5, 2022. Accessed September 14, 2022. https://www.astellas.com/en/news/26281

13. Neal-Perry G. A phase 3, randomized, placebo controlled, double blind study to investigate the long term safety and tolerability of fezolinetant in women seeking treatment for vasomotor symptoms associated with menopause (SKYLIGHT 4). Paper presented at: North American Menopause Society (NAMS) Annual Meeting 2022; October 12–15, 2022; Atlanta, GA.

14. Cano A. Secondary outcomes of a phase 3, randomised, placebo controlled, double blind study investigating the long term safety and tolerability of fezolinetant in women seeking treatment for vasomotor symptoms associated with menopause (SKYLIGHT 4). Paper presented at: International Menopause Society 18th World Congress on Menopause 2022; October 26–29, 2022; Lisbon, Portugal.

15. Lederman S, Shapiro CM, Stute P, Lee M, Wang X, Neal-Perry G. Phase 3 study of fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause [A132]. *Obstet Gynecol*. 2022;139:39S.doi:10.1097/01.AOG.0000825808.38519.3b

16. Neal-Perry G, Lederman S, Shapiro M, Stute P, Lee M, X. W. SKYLIGHT 1 ™ Phase 3 study of fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause. Paper presented at: American College of Obstetricians and Gynecologists Conference 2022; May 6–8, 2022; San Diego, CA.

17. Constantine GD, Revicki DA, Kagan R, et al. Evaluation of clinical meaningfulness of estrogen plus progesterone oral capsule (TX-001HR) on moderate to severe vasomotor symptoms. *Menopause*. 2019;26(5):513-9. doi:10.1097/GME.0000000000001261

18. Constantine GD, Simon JA, Kaunitz AM, et al. TX-001HR is associated with a clinically meaningful effect on severity of moderate to severe vasomotor symptoms in the REPLENISH trial. *Menopause*. 2020;27(11):1236-41. doi:10.1097/GME.0000000000001602

19. Cano A. Fezolinetant for treatment of moderate to severe vasomotor symptoms associated with menopause: Analysis of health related quality of life from the SKYLIGHT 1 ™and SKYLIGHT 2™studies. Paper presented at: International Menopause Society 18th World Congress on Menopause 2022; October 26–29, 2022; Lisbon, Portugal.

20. Lobo RA, Archer DF, Kagan R, et al. A 17beta-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: A randomized controlled trial. *Obstet Gynecol.* 2018;132(1):161-70. doi:10.1097/AOG.0000000000002645

21. Endrikat J, Graeser T, Mellinger U, Ertan K, Holz C. A multicenter, prospective, randomized, double-blind, placebo-controlled study to investigate the efficacy of a continuous-combined hormone therapy preparation containing 1mg estradiol valerate/2mg dienogest on hot flushes in postmenopausal women. *Maturitas.* 2007;58(2):201-7. doi:10.1016/j.maturitas.2007.08.004

22. Stevenson JC, Durand G, Kahler E, Pertyński T. Oral ultra-low dose continuous combined hormone replacement therapy with 0.5 mg 17β-oestradiol and 2.5 mg dydrogesterone for the treatment of vasomotor symptoms: Results from a double-blind, controlled study. *Maturitas.* 2010;67(3):227-32. doi:10.1016/j.maturitas.2010.07.002

23. Schürmann R, Holler T, Benda N. Estradiol and drospirenone for climacteric symptoms in postmenopausal women: A double-blind, randomized, placebo-controlled study of the safety and efficacy of three dose regimens. *Climacteric.* 2004;7(2):186-96. doi:10.1080/13697130410001713698

24. Lin SQ, Sun LZ, Lin JF, et al. Estradiol 1 mg and drospirenone 2 mg as hormone replacement therapy in postmenopausal Chinese women. *Climacteric.* 2011;14(4):472-81. doi:10.3109/13697137.2011.553971

25. Joffe H, Guthrie KA, LaCroix AZ, et al. Low-dose estradiol and the serotonin-norepinephrine reuptake inhibitor venlafaxine for vasomotor symptoms: A randomized clinical trial. *JAMA Intern Med.* 2014;174(7):1058-66. doi:10.1001/jamainternmed.2014.1891

26. Archer DF, Schmelter T, Schaefers M, Gerlinger C, Gude K. A randomized, double-blind, placebo-controlled study of the lowest effective dose of drospirenone with 17β-estradiol for moderate to severe vasomotor symptoms in postmenopausal women. *Menopause.* 2013;21(3):227-35. doi:10.1097/GME.0b013e31829c1431

27. Panay N, Ylikorkala O, Archer DF, Gut R, Lang E. Ultra-low-dose estradiol and norethisterone acetate: effective menopausal symptom relief. *Climacteric.* 2007;10(2):120-31. doi:10.1080/13697130701298107

28. Speroff L, Whitcomb RW, Kempfert NJ, Boyd RA, Paulissen JB, Rowan JP. Efficacy and local tolerance of a low-dose, 7-day matrix estradiol transdermal system in the treatment of menopausal vasomotor symptoms. *Obstet Gynecol.* 1996;88(4 Pt 1):587-92. doi:10.1016/0029-7844(96)00272-4

29. Diem SJ, LaCroix AZ, Reed SD, et al. Effects of pharmacologic and non-pharmacologic interventions on menopause-related quality of life: A pooled analysis of individual participant data from four MsFLASH trials. *Menopause.* 2020;27(10):1126-36. doi:10.1097/GME.0000000000001597

30. Caan B, LaCroix AZ, Joffe H, et al. Effects of estrogen or venlafaxine on menopause related quality of life in healthy postmenopausal women with hot flashes: A placebo-controlled randomized trial. *Menopause.* 2015;22(6):607-15. doi:10.1097/GME.0000000000000364

31. Simon JA, Kaunitz AM, Kroll R, Graham S, Bernick B, Mirkin S. Oral 17β-estradiol/progesterone (TX-001HR) and quality of life in postmenopausal women with vasomotor symptoms. *Menopause.* 2019;26(5):506-12. doi:10.1097/GME.0000000000001271

32. Prentice RL, Aragaki AK, Chlebowski RT, et al. Randomized trial evaluation of the benefits and risks of menopausal hormone therapy among women 50-59 years of age. *Am J Epidemiol.* 2021;190(3):365-75. doi:10.1093/aje/kwaa210

33. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297(13):1465-77. doi:10.1001/jama.297.13.1465

34. Simon JA, Portman DJ, Kaunitz AM, et al. Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: Two randomized controlled trials. *Menopause.* 2013;20(10):1027-35. doi:10.1097/GME.0b013e3182a66aa7

35. Freeman EW, Guthrie KA, Caan B, et al. Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. JAMA. 2011;305(3):267-74. doi:10.1001/jama.2010.2016

36. Evans ML, Pritts E, Vittinghoff E, McClish K, Morgan KS, Jaffe RB. Management of postmenopausal hot flushes with venlafaxine hydrochloride: A randomized, controlled trial. *Obstet Gynecol.* 2005;105(1):161-6. doi:10.1097/01.AOG.0000147840.06947.46

37. Archer DF, Seidman L, Constantine GD, Pickar JH, Olivier S. A double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy and safety for the treatment of vasomotor symptoms associated with menopause. *Am J Obstet Gynecol.* 2009;200(2):172.e1-10. doi:10.1016/j.ajog.2008.09.877

38. Speroff L, Gass M, Constantine G, Olivier S; Study 315 Investigators. Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms: A randomized controlled trial. *Obstet Gynecol.* 2008;111(1):77-87. doi:10.1097/01.AOG.0000297371.89129.b3

39. Bouchard P, Panay N, De Villiers TJ, et al. Randomized placebo-and active-controlled study of desvenlafaxine for menopausal vasomotor symptoms. *Climacteric.* 2012;15(1):12-20. doi:10.3109/13697137.2011.586445

40. Pinkerton JV, Archer DF, Guico-Pabia CJ, Hwang E, Cheng RFJ. Maintenance of the efficacy of desvenlafaxine in menopausal vasomotor symptoms: A 1-year randomized controlled trial. *Menopause.* 2013;20(1):38-46. doi:10.1097/GME.0b013e318274699f

41. Archer DF, Dupont CM, Constantine GD, Pickar JH, Olivier S; Study 319 Investigators. Desvenlafaxine for the treatment of vasomotor symptoms associated with menopause: A double-blind, randomized, placebo-controlled trial of efficacy and safety. *Am J Obstet Gynecol.* 2009;200(3):238.e1-10. doi:10.1016/j.ajog.2008.10.057

42. Pinkerton JV, Kagan R, Portman D, Sathyanarayana R, Sweeney M. Phase 3 randomized controlled study of gastro-retentive gabapentin for the treatment of moderate-to-severe hot flashes in menopause. *Menopause.* 2014;21(6):567-73. doi:10.1097/GME.0b013e3182a7c073

43. Reddy SY, Warner H, Guttuso Jr T, et al. Gabapentin, estrogen, and placebo for treating hot flushes: A randomized controlled trial. *Obstet Gynecol.* 2006;108(1):41-8. doi:10.1097/01.AOG.0000222383.43913.ed

44. Guttuso Jr T, Kurlan R, McDermott MP, Kieburtz K. Gabapentin's effects on hot flashes in postmenopausal women: A randomized controlled trial. *Obstet Gynecol.* 2003;101(2):337-45. doi:10.1016/s0029-7844(02)02712-6

45. Avis NE, Crawford SL, Greendale G, et al; Study of Women's Health Across the Nation. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med.* 2015;175(4):531-9. doi:10.1001/jamainternmed.2014.8063

46. Mirkin S, Graham S, Revicki DA, Bender RH, Bernick B, Constantine GD. Relationship between vasomotor symptom improvements and quality of life and sleep outcomes in menopausal women treated with oral, combined 17b-estradiol/progesterone. *Menopause.* 2019;26(6):637-42. doi:10.1097/GME.0000000000001294