New and Emerging Approaches for Treating VMS Associated with Menopause

Sponsorship and Support

This presentation is sponsored by

Primary Care Education Consortium

and supported by an educational grant from Bayer.

In collaboration with

FREE to JOIN!

PCMG Primary Care Metabolic Group

Join at **https://www.pcmg-us.org** for free CME, discounts on conferences and resources for clinicians interested in metabolic disorders.

Learning Objectives

Participants in this presentation should be able to…
Describe the burden and undertreatment of menopause-associated VMS and the impact of these symptoms on patients' quality of life.
Incorporate clinical safety and efficacy data for new and emerging therapies into treatment regimens for VMS.
Develop patient-specific therapeutic regimens for patients with VMS, including hormonal and non-hormonal therapies as appropriate.

Burden of VMS
and Risk Factors for VMS in Menopause

VMS and Menopause

- Vasomotor symptoms (VMS)[1]
  - Consist of hot flashes and night sweats
  - Considered primary symptoms of menopause
- Study of Women's Health Across the Nation (SWAN)[1,2]
  - 3302 midlife women across 5 racial and ethnic groups
  - Examines biological, physical, psychological, and social changes across the menopause transition

SWAN Study of Women's Health Across the Nation

1. El Khoudary SR, et al. *Menopause.* 2018;26(10):1213-1227. 2. SWAN Study: About SWAN, 2022. https://www.swanstudy.org/about/

Frequency and Symptom Burden of VMS

- 45%-97% of women experience VMS during menopause[1]
  - Symptoms often rated as moderate to severe
- Average daily frequency of symptoms is 4-5 occurrences per day[2]
  - Some report up to 20 occurrences in a day
- Occurrence of VMS persist for 7.4 years on average (SWAN data)[3]
  - Some studies report a 10-year average duration[4]
- The vast majority (up to 70%) of VMS remain untreated
  - Confusion and misinformation about safety and efficacy of treatments
  - Lack of menopause training among clinicians[5]

1. Makara-Studzińka MT, et al. *Prz Menopauzalny*. 2014;13(3):203-211. 2. Avis NE, et al. *Obstet Gynecol Clin North Am*. 2018;45(4):629-640. 3. Avis NE, et al. *JAMA Intern Med*. 2015;175(4):531-539. 4. Freeman EW, et al. *Obstet Gynecol*. 2011;117(5):1095-1104. 5. Hsieh E, et al. *J Womens Health (Larchmt)*. 2013;22(8):667-672.

Impact of VMS on Health-Related Outcomes

- VMS are associated with increased cardiovascular risk
  - Higher blood pressure[1]
  - Higher BMI[1]
  - Higher cholesterol levels[1]
  - Higher rate of subclinical cardiovascular disease[2]
  - Associated with increased aortic calcification[3]
- VMS are also associated with higher rates of bone loss and bone turnover[4]

BMI, body mass index

1. Gast GM, et al. *Hypertension*. 2008;51(6):1492-1498. 2. Thurston RC, et al. *Circulation*. 2008;118(12):1234-1240. 3. Thurston RC, et al. *Menopause*. 2018;25(11):1291-1296. 4. Crandall CJ, et al. *BJOG*. 2012;119(1):40-50.

Risk Factors for VMS[1,2]

- Low education
- Smoking
- Negative affect
- Menopause status
- Anxiety or depression prior to menopause
- Higher sensitivity to symptoms
- Anti-endocrine therapy
- Black race

Mixed or no evidence
- Physical activity
- Diet
- Alcohol consumption

Obesity
- Higher BMI is associated with
  - More frequent VMS in early menopause
  - Less frequent VMS in late menopause

1. Thurston RC and Joffe H. *Obstet Gynecol Clin North Am*. 2011;38(3):489-501. 2. Avis NE, et al. *Obstet Gynecol Clin North Am*. 2018;45(4):629-640.

The Primary Care Clinician's Role
Identification, Treatment, and Referral

The Role of PCCs in VMS Care[1]

- Many primary care clinicians (PCCs) have little experience in treating women undergoing menopause.
- However, PCCs are often the first to encounter complaints about VMS and other symptoms of menopause.
- PCCs can also consider asking questions that will help elicit VMS symptoms.
- Patients who need specialist care may be referred.

Questions that can elicit VMS symptoms[1]
Any changes in your periods?
Are you having any hot flashes?
Any vaginal dryness or pain, or any sexual concerns?
Any bladder issues or incontinence?
How is your sleep?
How is your mood?

1. Goldstein S. *Can Fam Physician*. 2017;63(4):295-298.

Identification and Care of VMS in Clinical Settings

- Menopause care should be the shared responsibility of primary care and gynecology.
  - Many patients can be successfully treated in primary care
- Clinicians should consider:
  - Paying particular attention to women aged 45-60 years
  - Incorporating questions about VMS in Review of Systems: make it routine
  - Probing for other symptoms patients may not volunteer beyond VMS: heart palpitations, mood, sexual health concerns, sleep
  - Engaging patients in a conversation about risks and benefits of hormone therapy and discuss other options
  - Having resources available

Patient Case

A 55-year-old woman presents to her primary care clinic with complaints of significant night sweats and hot flashes she thinks are associated with menopause. She is interested in starting therapy if there is something that can help. She expresses concerns about ongoing low libido and wants to avoid any therapy that would worsen this.

Impact on Quality of Life

VMS and associated psychosocial impairment during the menopausal transition[1-3]:

Vasomotor Symptoms	Related Psychosocial Impairment
Cognitive deficits	Poor concentration, verbal memory problems
Mood swings	Irritability, sadness, tension
Sleep disturbances	Insomnia, sleep apnea
Social impairment	Disruption of family relationships, social isolation
Work-related difficulties	Reduced productivity

Other quality of life impairments include embarrassment, anxiety, and fatigue.

1. Utian WH. *Health Qual Life Outcomes*. 2005;3:47. 2. Baker FC, et al. *Nat Sci Sleep*. 2018;10:73-95. 3. Parish SJ, et al. *Menopause*. 2018;25(8):937-949.

Patient Case

A 55-year-old woman presents to her primary care clinic with complaints of significant night sweats and hot flashes she thinks are associated with menopause. She is interested in starting therapy if there is something that can help. She expresses concerns about ongoing low libido and wants to avoid any therapy that would worsen this.

What additional questions/assessments might be helpful in evaluating this patient's VMS?

Undertreatment of VMS

Consequences and Barriers

Delays in Care

Based on data from 1016 women initially presenting with menopausal symptoms (including VMS):

50% delayed seeking care for ≥6 months

40% had no prescription treatment for menopausal symptoms

27% taking only nonprescription medications or supplements

DePree B, et al. *Menopause*. 2022;30(1):70-79.

Low Use of Available Therapies

Percentage of postmenopausal women with moderate to severe VMS who are receiving treatment[1]:

7% taking hormonal therapies*

4% taking nonhormonal prescription medications

15% taking nonprescription medications or supplements

*Compounded bioidentical hormone therapy not included.

1. Kroll R, et al. 2020 NAMS Virtual Annual Meeting. *Menopause*. 2020;27(12):1447-1475.

Barriers to Treating VMS

- Many clinicians who regularly see patients with VMS lack confidence managing these symptoms
  - In one study, 46% of oncology clinicians who treat women with breast cancer did not feel confident in managing hot flashes[1]
- WHI 2002 study stigma[2]
  - Raised concerns about long-term use of hormone therapy
- Lack of clinicians' formalized training in managing VMS[3]
  - Changes in residency curriculum may be needed

1. Cole KM, et al. *Breast Cancer Res Treat.* 2021;22:1-8. 2. Rossouw JE, et al. *JAMA.* 2002;288(3):321-333. 3. Kling JM, et al. *Mayo Clin Proc.* 2019;94(2):242-253.

Barriers to Treating VMS (continued)

- **Patient barriers:**
  - Discomfort reporting symptoms to their provider
  - Fear of estrogen
  - Confusion around difference between FDA approved hormone products and bioidentical/compounded hormone products
- **Clinician barriers:**
  - Lack of time/short office visits and lack of adequate reimbursement for time-based consultations/shared decision making
  - Lack of training in menopause medicine
  - Lack of awareness of available option for hormone therapy
  - Fear of use of available therapies, fear of estrogen
- **Therapy barriers:**
  - WHI study data leading to confusion/misinformation
  - FDA mandated estrogen risks on label

WHI, Women's Health Initiative

Treatments for VMS in Menopause

Current, New, and Emerging Therapies

Physiology of VMS

Not completely understood – likely an interplay of multiple physiologic systems[1,2]:

Reproductive hormones	• VMS onset during dramatic hormone changes of menopausal transition • Therapeutic role of exogenous estrogen • Higher FSH and lower E2/E1C may be associated with VMS • All women have hormone changes at menopause, but not all have VMS
Thermoregulatory	• Narrowing of thermoneutral zone where core body temperature is maintained • Small changes in core body temperature could exceed zone and trigger sweating and peripheral vasodilation (hot flashes) • E2 administration widens thermoneutral zone
Genetics	• Variants in ER genes can predict VMS • SNPs in genes that affect estrogen synthesis and metabolism

FSH, follicle stimulating hormone; E2, estradiol; E1C, estrone conjugates; ER, estrogen receptor; SNP, single nucleotide polymorphism

1. Thurston RC and Joffe H. *Obstet Gynecol Clin North Am*. 2011;38(3):489-501. 2. Rapkin AJ. *Am J Obstet Gynecol*. 2007;196(2):97-106.

Physiology of VMS

Not completely understood – likely an interplay of multiple physiologic systems[1,2]:

Reproductive hormones	• VMS onset during dramatic hormone changes of menopausal transition • Therapeutic role of exogenous estrogen • Higher FSH and lower E2/E1C may be associated with VMS • All women have hormone changes at menopause, but not all have VMS
Thermoregulatory	• Narrowing of thermoneutral zone where core body temperature is maintained • Small changes in core body temperature could exceed zone and trigger sweating and peripheral vasodilation (hot flashes) • E2 administration widens thermoneutral zone
Genetics	• Variants in ER genes can predict VMS • SNPs in genes that affect estrogen synthesis and metabolism

Hormonal therapy

1. Thurston RC and Joffe H. *Obstet Gynecol Clin North Am*. 2011;38(3):489-501. 2. Rapkin AJ. *Am J Obstet Gynecol*. 2007;196(2):97-106.

Hormonal Therapy for VMS

The North American Menopause Society (NAMS) position statement on hormone therapy[1]:

- "Hormone therapy remains the most effective treatment for VMS"
- "The risks of HT differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used"

Treatment should be individualized to minimize risk and maximize benefits and be reevaluated periodically.

1. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. *Menopause*. 2017;24(7):728-753.

Hormonal Therapy for VMS

The NAMS position statement on hormone therapy[1]:

- "For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome VMS and for those at elevated risk for bone loss or fracture"
- "For women who initiate HT more than 10 or 20 years from menopause onset or are aged 60 years or older, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia"

1. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. *Menopause*. 2017;24(7):728-753.

Benefits of Hormonal Therapy for VMS

- Relief of VMS
- Reduced nighttime awakenings
- Improved genitourinary symptoms (if present)
- Improved vaginal lubrication, blood flow, and sensation of vaginal tissue
- Improved health-related QOL and menopause-specific QOL
- Reduced bone loss

QOL, quality of life

1. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. *Menopause*. 2017;24(7):728-753.

Hormonal Therapy and CV Risk

2017: 18-year follow-up on WHI randomized trials[1]

- Hormone therapy with estrogen alone or estrogen + progestogen
- No increase in
  - All-cause mortality
  - CV disease mortality
  - Cancer mortality

2020: AHA Scientific Statement[2]

- Presence of increased cardiovascular disease risk after menopause
- CV benefit of hormone therapy when initiated in women <60 years

CV, cardiovascular

1. Manson JE, et al. *JAMA*. 2017;318(10):927-938. 2. El Khoudary SR, et al. *Circulation*. 2020;142:e506-e532.

Hormonal Medications for Treatment of VMS

The AAFP recommends that systemic estrogen therapy, alone or in combination with progestogen is the **most effective therapy for hot flashes** and highlights that **this is an FDA-approved indication**.[1]

AAFP, American Academy of Family Physicians

[a]Bioidentical product available, or product is a bioidentical

1. Hill DA, et al. *Am Fam Physician*. 2016;94(11):884-889.

Route of Administration	Medication, Brand Name (generic name)
Oral	Enjuvia (conjugated estrogen)
	[a]Estrace (estradiol)
	Menest (esterified estrogen)
	Premarin (conjugated estrogen)
	Activella (estradiol/norethindrone acetate)
	Angeliq (estradiol/drospirenone)
	Duavee (conjugated equine estrogen/bazedoxefine)
	Femhrt (estradiol/norethindrone acetate)
	Prefest (estradiol/norgestimate)
	Premphase (conjugated estrogen/medroxyprogesterone)
	Prempro (conjugated estrogen/medroxyprogesterone)
	[a]Bijuva (estradiol and progesterone)
Transdermal Patch	[a]Alora (estradiol)
	[a]Climara (estradiol)
	[a]Minivelle (estradiol)
	[a]Vivelle Dot (estradiol)
	Climara Pro (estradiol/levonorgestrel)
	Combipatch (estradiol/norethindrone acetate)
Transdermal Gel	[a]Divigel (estradiol)
	[a]Elestrin (estradiol)
	[a]Estrogel (estradiol)
Transdermal Spray	[a]Evamist (estradiol)
Vaginal	[a]Femring (estradiol)

Physiology of VMS

Not completely understood – likely an interplay of multiple physiologic systems[1,2]:

Reproductive hormones	• VMS onset during dramatic hormone changes of menopausal transition • [redacted] VMS • All women have hormonal changes at menopause, but not all have VMS
Thermoregulatory	• Narrowing of thermoneutral zone where core body temperature is maintained • Small changes in core body temperature could exceed zone and trigger sweating and peripheral vasodilation (hot flashes) • E2 administration widens thermoneutral zone
Genetics	• Variants in ER genes can predict VMS • SNPs in genes that affect estrogen synthesis and metabolism

Neurokinin 3 receptor (NK3R) antagonists

1. Thurston RC and Joffe H. *Obstet Gynecol Clin North Am*. 2011;38(3):489-501. 2. Rapkin AJ. *Am J Obstet Gynecol*. 2007;196(2):97-106.

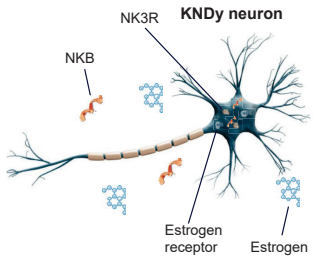
Therapeutic Rationale for NK3R Antagonists

Thermoregulatory Homeostasis

1. KNDy neurons contribute to body temperature control inside the thermoregulatory center in the hypothalamus
2. KNDy neurons are inhibited by estrogen and stimulated by NKB

During the Transition to Menopause

3. Declining estrogen in menopause leads to uninhibited NKB-mediated stimulation of KNDy neurons
4. Heat dissipation effectors are triggered from the thermoregulatory center, experienced as VMS



KNDy, kisspeptin, neurokinin B, dynorphin A; NKB, neurokinin B

1. Menown SJ and Tello JA. *Adv Ther*. 2021;38(10):5025-5045. 2. Padilla SL, et al. *Cell Rep*. 2018;24(2):271-277. 3. Krajewski-Hall SJ, et al. *Temperature*. 2018;5(1):56-69.

Therapeutic Rationale for NK3R Antagonists

?

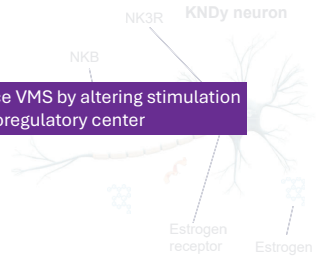
Thermoregulatory Homeostasis

1. KNDy neurons contribute to body temperature control inside the thermoregulatory center in the hypothalamus
2. KNDy neurons are inhibited by estrogen and stimulate NKB

NK3R antagonists are thought to reduce VMS by altering stimulation of neurons in the hypothalamic thermoregulatory center

During the Transition to Menopause

1. Declining estrogen in menopause leads to uninhibited NKB-mediated stimulation of KNDy neurons
2. Heat dissipation effectors are triggered from the thermoregulatory center, experienced as VMS



KNDy, kisspeptin, neurokinin B, dynorphin A; NKB, neurokinin B

1. Menown SJ and Tello JA. *Adv Ther*. 2021;38(10):5025-5045. 2. Padilla SL, et al. *Cell Rep*. 2018;24(2):271-277. 3. Krajewski-Hall SJ, et al. *Temperature*. 2018;5(1):56-69.

NK3R Antagonists Clinical Data

Several NK3R antagonists are in development.

Notable NK3R antagonists:

1. Fezolinetant, a selective NK3R antagonist (FDA approved)
   - Phase 3 trials: SKYLIGHT 1 (NCT04003155), SKYLIGHT 2 (NCT04003142), SKYLIGHT 4 (NCT04003389), MOONLIGHT 1 (NCT04234204), and MOONLIGHT 3 (NCT04451226)
2. Elinzanetant, a nonselective NK1R/NK3R antagonist (Phase 3)
   - Phase 3 trials: OASIS-1 (NCT05042362), OASIS-2 (NCT05099159), OASIS-3 (NCT05030584)

Fezolinetant – SKYLIGHT 1 (Phase 3)[1]

Patients	• N = 527 • Women aged 40–65 years with moderate-to-severe VMS • Average of 7 hot flashes per day
Methods	• Double-blind, placebo-controlled randomized phase 3 trial • 1:1:1 to fezolinetant 45 mg daily, fezolinetant 30 mg daily or placebo • Placebo controlled for 12-weeks, followed by a 40-week blinded extension
Results	• Both doses of fezolinetant showed significant reduction in VMS frequency and severity at weeks 4 and 12 compared to placebo • Improvements sustained over 52 weeks • Treatment emergent adverse effects occurred in 43% of patients in the fezolinetant 45 mg group, 37% in the fezolinetant 30 mg group, and 45% in the placebo group
Conclusions	• Fezolinetant may be an option for non-hormonal treatment for VMS associated with menopause and warrants further investigation

1. Lederman S, et al. *Lancet*. 2023;401(10382):1091-1102.

Fezolinetant – SKYLIGHT 2 (Phase 3)[1]

Patients	• N = 500 • Women aged 40–65 years with moderate-to-severe VMS • Minimum average of 7 hot flashes per day
Methods	• Double-blind, placebo-controlled randomized phase 3 trial • 1:1:1 to fezolinetant 45 mg daily, fezolinetant 30 mg daily or placebo • Randomized for 12 weeks with a 40-week active treatment extension
Results	• Both doses of fezolinetant showed significant reduction in VMS frequency and severity at weeks 4 and 12 compared to placebo • Improvements sustained over 52 weeks • Treatment-emergent adverse events reported in 36% of patients receiving fezolinetant 45 mg, 40% for fezolinetant 30 mg, and 32% for placebo
Conclusions	• Fezolinetant 30 mg and 45 mg daily were effective and well-tolerated for treating moderate-to-severe VMS associated with menopause

1. Johnson KA, et al. *J Clin Endocrinol Metab*. 2023;108(8):1981-1997.

Fezolinetant – SKYLIGHT 4 (Phase 3 Safety)[1]

Patients	• N = 1830 • Women who were postmenopausal and seeking treatment for VMS associated with menopause
Methods	• Randomized, double-blind, 52-week safety study • 1:1:1 to fezolinetant 45 mg daily, fezolinetant 30 mg daily or placebo

Results	• Treatment-emergent adverse events:
	  • 63.9% fezolinetant 45 mg
	  • 67.9% fezolinetant 30 mg
	  • 64.1% placebo
	• Similar treatment-emergent adverse events leading to discontinuation across groups

Conclusions	• SKYLIGHT 4 confirms the 52-week safety and tolerability of fezolinetant

1. Neal-Perry G, et al. *Obstet Gynecol*. 2023;141(4):737-747.

Fezolinetant –DAYLIGHT (Phase 3b)[1]

Patients	• N = 452 (full analysis set); 370 (completers) • Women aged 40–65 years with moderate-to-severe VMS associated with menopause who were considered unsuitable for hormone therapy, had discontinued hormone therapy, or who chose not to use hormone therapy
Methods	• Double-blind, placebo-controlled randomized phase 3b trial • 1:1 to fezolinetant 45 mg daily or placebo for 24 weeks
Results	• At week 24, fezolinetant significantly reduced the frequency and severity of VMS and had a greater reduction in sleep disturbance compared to placebo (P <.001 for all comparisons) • Treatment-emergent adverse events were similar between both groups
Conclusions	• Fezolinetant 45 mg daily was efficacious and well tolerated over a 6-month period for treating moderate-to-severe VMS in patients considered unsuitable for hormone therapy

1. Schaudig K, et al. *BMJ*, 2024;387:e079525.

Elinzanetant – OASIS 1 and 2 (Phase 3)[1]

Patients	• N = 396 (OASIS 1) • N = 400 (OASIS 2) • Postmenopausal with moderate-to-severe VMS
Methods	• Double-blind, placebo-controlled randomized phase 3 trials • Patients received elinzanetant 120 mg for 26 weeks or matching placebo for 12 weeks, followed by elinzanetant 120 mg for 14 weeks
Results	• Elinzanetant significantly reduced VMS frequency and severity at week 4 and week 12 compared to placebo • Elinzanetant improved sleep disturbances and menopause-related quality of life at week 12 • Treatment-emergent adverse events in 51.3% of elinzanetant group and 48.5% of the placebo group (OASIS 1) • Treatment-emergent adverse events in 44.3% of the elinzanetant group and 38.2% of the placebo group (OASIS 2)
Conclusions	• Elinzanetant was well-tolerated and efficacious for moderate-to-severe VMS associated with menopause

1. Pinkerton JV, et al. *JAMA*. 2024;332(16):1343-1354.

Elinzanetant – OASIS 3 (Phase 3)

Patients	• N = 628 • Postmenopausal between 40 and 65 years of age with moderate-to-severe VMS
Methods	• Double-blind, placebo-controlled randomized phase 3 trial • Patients randomized 1:1 to elinzanetant 120 mg or placebo for 52 weeks
Results	• Baseline VMS: 6.7 episodes (elinzanetant), 6.8 episodes (placebo) • At week 12, the number of VMS episodes was reduced to 1.6 (elinzanetant) and 3.4 (placebo), *P* <.0001 • Treatment-emergent adverse reactions occurred in 70.0% patients in the elinzanetant group and 61.1% patients in the placebo group
Conclusions	• Elinzanetant was efficacious for treating menopause-associated VMS, with a favorable long-term safety profile

1. Panay N, et al. In: Proceedings and abstracts of the 2024 Annual Meeting of the Menopause Society, September 11–14, 2024. Chicago: Menopause Society, 2024. Accessed June 3, 2025. https://menopause.org/wp-content/uploads/2024/09/2024-Oral-and-Poster-Presentation-Abstracts.pdf

Elinzanetant – OASIS 4 (Phase 3)

Patients	• N = 474 • Women 18 to 70 years of age with moderate-to-severe VMS associated with endocrine therapy for hormone receptor-positive breast cancer or prevention
Methods	• Double-blind, placebo-controlled randomized phase 3 trial • Randomized 2:1 to elinzanetant 120 mg once daily for 52 weeks or placebo once daily for 12 weeks followed by once daily elinzanetant 120 mg once daily for 40 weeks
Results	• Baseline mean daily frequency of moderate-to-severe VMS was 11.4 episodes (elinzanetant group) and 11.5 episodes (placebo-elinzanetant group) • At week 4, mean change was -6.5 episodes (elinzanetant) versus -3.0 episodes (placebo), *P* <.001 • At week 12, the mean change was -7.8 episodes (elinzanetant) versus -4.2 episodes (placebo), *P* <.001 • Adverse events were 69.8% (elinzanetant) and 62.0% (placebo-elinzanetant)
Conclusions	• Elinzanetant led to a significantly lower frequency of VMS associated with endocrine therapy compared to placebo

1. Pinkerton JV, et al. *JAMA*. 2024;332(16):1343-1354.

Other Investigational Agents and Mechanisms

Agent	Mechanism
Orexin-A receptor antagonist (suvorexant)[1]	• Orexin-A modulates thermoregulation and promotes wakefulness • Potentially mediates the sleep disruption patterns seen in menopause
TRPM8 antagonists (elismetrep)[2]	• TRPM8 is a member of the TRP cation channel family • Plays a key role in the sensation of environmental cold • TRPM8 antagonism may reduce VMS by using the body's natural methods of passive cooling to prevent an increase in core temperature

TRPM8, transient receptor potential melastatin 8; TRP, transient receptor potential

1. Rahman SA, et al. *Sleep*. 2022;45(3):zsac007. 2. Kingsberg S, et al. 2020 NAMS Virtual Annual Meeting. *Menopause*. 2020;27(12):1447-1475.

Tamoxifen and SSRIs/SNRIs: CYP2D6 Inhibition[1-4]

Potent Inhibitors	Moderate Inhibitors	Weak Inhibitors	No CYP2D6 Activity
Fluoxetine	Sertraline	Citalopram	**Venlafaxine**
Paroxetine	Duloxetine	Escitalopram	**Desvenlafaxine**
Bupropion	Fluvoxamine		**Mirtazapine**

AVOID WITH TAMOXIFEN → **PREFERRED WITH TAMOXIFEN**

Alternative Therapies

- Valerian extracts, genistein (an isoflavone), and red clover should be avoided in tamoxifen users
- Black cohosh does not inhibit CYP2D6

CYP, cytochrome P450

1. Day R, et al. *Ann N Y Acad Sci*. 2001;949:143-150. 2. Jin Y, et al. *J Clin Oncol*. 2008;26(36):5849-5854. 3. Crandall C, et al. *Menopause*. 2004;11(5):519-530. 4. Desmarais JE and Looper KJ. *Maturitas*. 2010;67(4):296-308.

Nonpharmacologic and Alternative Therapies[1]

- Limited evidence for nonpharmacologic and alternative therapies
- Lack of supervision of herbal products by the FDA

Interventions with mixed or limited data

Relaxation
Mindfulness
Cognitive behavioral therapy
Some soy-based products
Bee pollen
Black cohosh

1. Johnson A, et al. *J Evid Based Integr Med*. 2019;24:2515690X19829380.

Nonhormonal Medications Used for VMS

Therapeutic Class	Brand Name (generic name)
NK3R Antagonists	Veozah (fezolinetant)*
SSRIs	Celexa (citalopram)
	Lexapro (escitalopram)
	Brisdelle (paroxetine)*
SNRIs	Pristiq (desvenlafaxine)
	Cymbalta (duloxetine)
	Effexor (venlafaxine)
Central alpha-2 agonist	Catapres (clonidine)
Anticonvulsants	Neurontin (gabapentin)
	Lyrica (pregabalin)
Antispasmodic	Ditropan (oxybutynin)

*FDA approved for VMS

Developing Patient-Specific Regimens for VMS

Clinical Decision-Making

Nonhormonal Prescription Therapies[1,2,3]

Intervention	Comments
SSRI/SNRI • Citalopram • Desvenlafaxine • Duloxetine • Escitalopram • Paroxetine ○ FDA approved • Venlafaxine	Titrate from low dose Caution with drug interactions with tamoxifen Reduced libido Weight gain
Clonidine	Adverse events including dizziness, hypotension, and rebound hypertension limit usefulness
Gabapentin, pregabalin	Neurologic effects, weight gain
Oxybutynin[4,5]	Dry mouth, abdominal pain, difficulty urinating
Stellate ganglion block	C6-T2 anterior cervical spine block; larger studies needed

SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

1. Hill DA, et al. *Am Fam Physician*. 2016;94(11):884-889. 2. Rapkin AJ. *Am J Obstet Gynecol*. 2007;196(2):97-106. 3. Iyer TK, et al. *Cleve Clin J Med*. 2024;91(4):237-244. 4. Leon-Ferre RA, et al. *JNCI Cancer Spectr*. 2019;4(1):pkz088. 5. Simon JA, et al. *Menopause*. 2016;23(11):1214-1221.

Individualizing Therapy for VMS

Clinical decision-making[1]

Does the patient have moderate-to-severe hot flashes and/or night sweats, with inadequate response to behavioral and lifestyle interventions?

YES

Is the patient free of breast cancer, endometrial cancer, venous thromboembolism, stroke, cardiovascular disease, and other contraindications?

Would patient consider hormone therapy if recommended by clinician?

1. Manson JE, et al. *Menopause*. 2015;22(3):247-253.

Individualizing Therapy for VMS

Clinical decision-making[1]

Vasomotor Symptoms Pathway

Is the patient free of breast cancer, endometrial cancer, venous thromboembolism, stroke, CV disease, and other contraindications?

Would patient consider hormone therapy if recommended by clinician?

YES

Consider number of years from menopause and cardiovascular risk

NO

Consider nonhormonal options

1. Manson JE, et al. *Menopause*. 2015;22(3):247-253.

Individualizing Therapy for VMS

?

Clinical decision-making[1]

Vasomotor Symptoms Pathway

Is the patient free of breast cancer, endometrial cancer, venous thromboembolism, stroke, CV disease, and other contraindications?

Hormone therapy is not recommended for patients with a history of breast cancer, endometrial cancer, thromboembolism, stroke, or CV disease.

YES

Consider number of years from menopause and cardiovascular risk

NO

Consider nonhormonal options

1. Manson JE, et al. *Menopause*. 2015;22(3):247-253.

Remember this Question?

The following patients all present with complaints of menopause-related VMS. For which patient would you recommend pharmacologic treatment with hormone therapy?

A. A 62-year-old woman who has moderate VMS and says that she is afraid of getting a blood clot from taking hormones.

B. A 69-year-old woman who has a recurrence of VMS; when she took estrogen in the past, it was the only thing that helped with her symptoms. She has hypertension, hyperlipidemia, and diabetes.

C. A 51-year-old woman with a history of breast cancer, taking tamoxifen. She fears weight gain and sexual side effects from drugs but wants to try something for VMS.

D. A 54-year-old woman with severe menopausal VMS, hypothyroidism, and no history of cancer or thromboembolism.

Individualizing Therapy for VMS

Clinical decision-making[1]

Vasomotor Symptoms Pathway: Hormonal Therapy

Consider number of years from menopause and CV risk

↓

Assess CV risk and time since menopause onset

CV risk	Years since menopause onset	
	≤10	>10
Low	Hormone therapy OK	Consider hormone therapy cautiously with shared decision-making
Moderate	Hormone therapy OK (choose transdermal)	Avoid hormone therapy
High	Avoid hormone therapy	Avoid hormone therapy

1. Manson JE, et al. *Menopause*. 2015;22(3):247-253.

Individualizing Therapy for VMS

Clinical decision-making[1]

Vasomotor Symptoms Pathway: Hormonal Therapy

CV risk	Years since menopause onset	
	≤10	>10
Low	Hormone therapy OK	Consider hormone therapy cautiously with shared decision-making
Moderate	Hormone therapy OK (choose transdermal)	Avoid hormone therapy
High	Avoid hormone therapy	Avoid hormone therapy

↓

- If hormone therapy initiated, use estrogen + progestogen for women with a uterus, estrogen only for women without a uterus
- Monitor and adjust therapy based on symptomatic response and ongoing cancer, CV, and osteoporosis risk assessment

1. Manson JE, et al. *Menopause*. 2015;22(3):247-253.

Individualizing Therapy for VMS

Clinical decision-making[1]

Vasomotor Symptoms Pathway: Nonhormonal Therapy

Is the patient free of breast cancer, endometrial cancer, venous thromboembolism, stroke, cardiovascular disease, and other contraindications, and interested in hormone therapy?

↓ **NO**

Select nonhormonal therapy based on effectiveness, comorbidities, drug interactions, and adverse effects profile

1. Manson JE, et al. *Menopause*. 2015;22(3):247-253.

Individualizing Therapy for VMS

Clinical decision-making[1]

Vasomotor Symptoms Pathway: Nonhormonal Therapy

Select nonhormonal therapies based on effectiveness, comorbidities, drug interactions, and adverse effects profile

Medication	Comments
SSRI/SNRI • Citalopram • Desvenlafaxine • Escitalopram • Paroxetine • Venlafaxine	• Drug interactions with tamoxifen (paroxetine) • Reduced libido • Weight gain

Medication	Comments
Gabapentin Pregabalin	• Neurologic effects • Weight gain
Oxybutynin	• Dry mouth • Abdominal pain • Difficulty urinating
Clonidine	• Dizziness • Hypotension • Rebound hypertension

1. Manson JE, et al. *Menopause*. 2015;22(3):247-253.

Individualizing Therapy for VMS

Clinical decision-making[1]

Vasomotor Symptoms Pathway: Nonhormonal Therapy

Select nonhormonal therapies based on effectiveness, comorbidities, drug interactions, and adverse effects profile

Medication	Comments
SSRI/SNRI • Citalopram • Desvenlafaxine • Escitalopram • Paroxetine • Venlafaxine	• Drug interactions with tamoxifen (paroxetine) • Reduced libido • Weight gain
Consider an FDA-approved NK3R antagonist	

Medication	Comments
Gabapentin Pregabalin	• Neurologic effects • Weight gain
Oxybutynin	• Dry mouth • Abdominal pain • Difficulty urinating
Clonidine	• Dizziness • Hypotension • Rebound hypertension

1. Manson JE, et al. *Menopause*. 2015;22(3):247-253.

Visit our VMS in Menopause toolkit at

https://www.pcmg-us.org/toolkit/vms

or use QR code below for additional resources, links to references used in the presentation, download the slide deck or to watch a webinar of this presentation.

Now back to our case study…

Patient Case (continued)

A 55-year-old woman presents to her primary care clinic with complaints of significant night sweats and hot flashes she thinks are associated with menopause. She is interested in starting therapy if there is something that can help. She expresses concerns about ongoing low libido and wants to avoid any therapy that would worsen this.

Upon further questioning and evaluation, you discover that she has a history of thromboembolism.

Patient Case (continued)

A 55-year-old woman presents to her primary care clinic with complaints of significant night sweats and hot flashes she thinks are associated with menopause. She is interested in starting therapy if there is something that can help. She expresses concerns about ongoing low libido and wants to avoid any therapy that would worsen this.

Upon further questioning and evaluation, you discover that she has a history of thromboembolism.

What individualized treatment strategy might you recommend for this patient's VMS symptoms?