Understanding and Managing Vasomotor Symptoms

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- **University of Virginia Health**
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- **Past President SAAOG**

SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS • EST. 1938

UVA Health
University Medical Center

Disclosures

During this talk, I may mention the use of medications for both U.S. Food and Drug Administration (FDA)-approved and non-FDA-approved indications.

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Consultant- Bayer HealthCare Pharmaceuticals Inc, Pfizer, and Merck
Editorial Boards: Menopause, Climacteric, J Women's Health, Contemporary ObGyn

VASOMOTOR SYMPTOMS- hot flashes and night sweats

VMS are the most common and bothersome symptoms,
hallmark symptoms of hot flashes and night sweats-

Hot flashes are described as episodes of sudden intense sensation of heat,
often starting in the upper chest area, that may last 1 to 5 minutes

- May be accompanied by chills, sweating, feelings of dread, or palpitations
- Race, ethnicity, comorbidities, lifestyle factors, psychosocial factors affect menopause symptoms

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- For 10 to 15 % of women, severe hot flashes disrupt normal functions, such as leading a meeting, sticking to a schedule, getting adequate sleep
- Associated often with sleep disruption or mood change

FDA definition of VMS

Mild: sensation of heat without sweating

Moderate: sensation of heat with sweating, able to continue activity

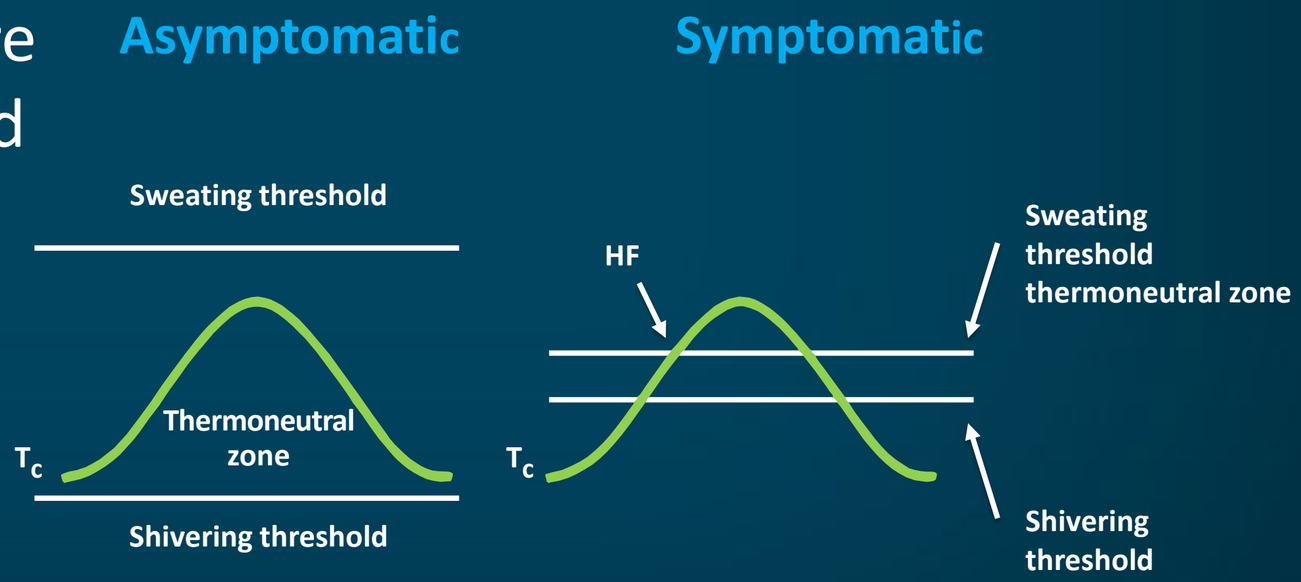
Severe: sensation of heat with sweating, causing cessation of activity

FDA = US Food and Drug Administration; VMS = vasomotor symptoms.

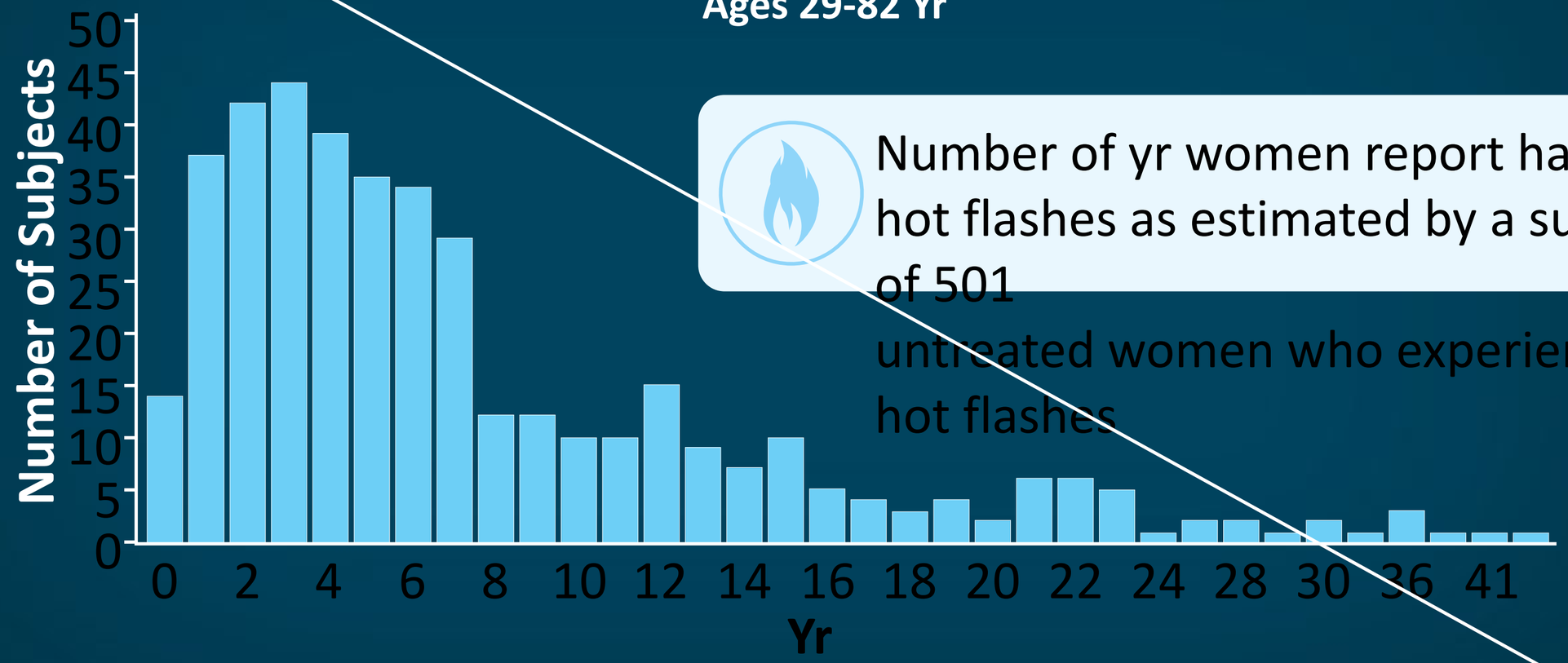
FDA. Guidance for industry, 2003 (https://www.fda.gov/media/71359/download). Accessed 5/1/2024.

Physiologic Mechanisms of VMS

- VMS involve the vasodilation of cutaneous vessels; increased skin temperatures
  - Vasodilation and sweating occur as heat dissipation
- Related to small fluctuations in core body temperature superimposed on an extremely narrow thermoneutral zone
- Triggered when core body temperature rises above upper (sweating) threshold
- Shivering occurs when core body temperature falls from elevated level to a level below the lower threshold of thermoneutral zone



Freedman RR, Blacker CM. *Fertil Steril.* 2002;77:487-490. Freedman RR, Subramanian M. *Menopause.* 2005;12:156-159. Freedman RR. *Semin Reproductive Med.* 2005;32:117-125.

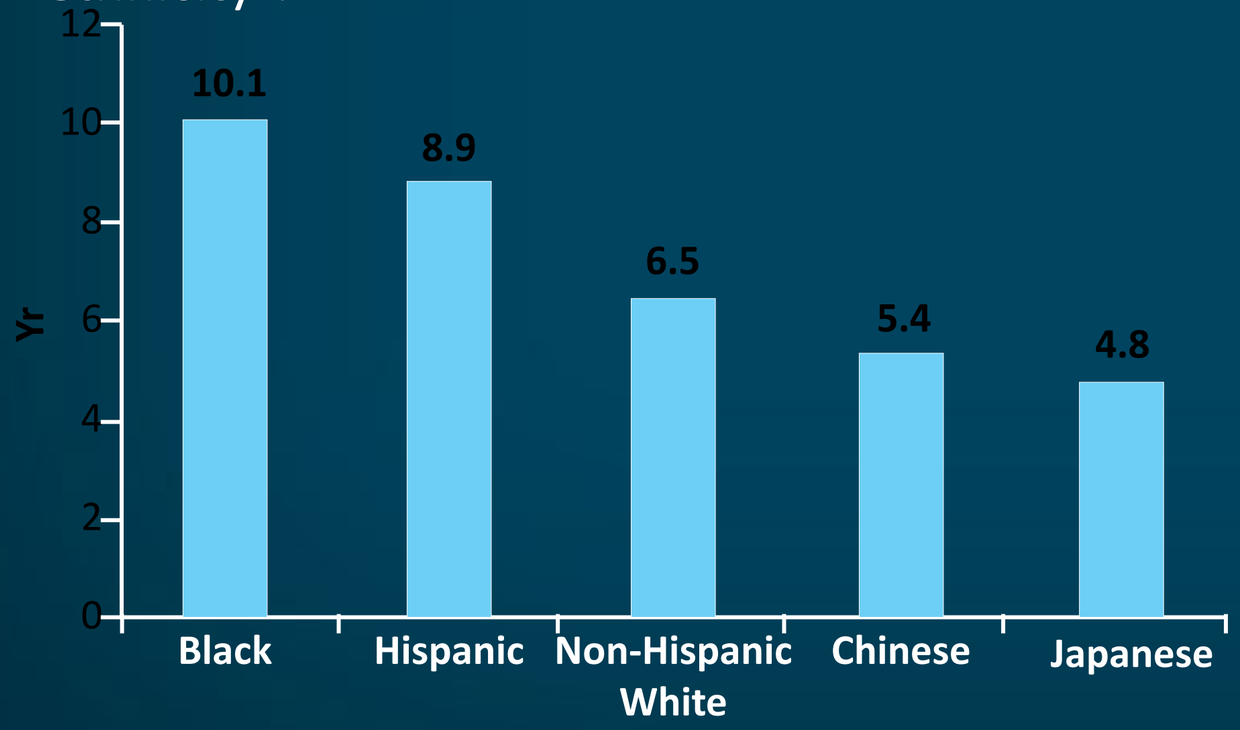


Mean age of *natural* menopause was 49.5 yr; mean age of *surgical* menopause 43.7 yr.

Kronenberg . Ann N Y Acad Sci. 1990;592:52.

Culturally Sensitive Care

- SWAN study reported median VMS duration in women varied according to race and ethnicity[1]:



- Cultural stereotypes, the woman's background, and how women deal with menopause-related changes, direct how women experience menopause[2,3]
  - Culturally sensitive approaches to menopause care:
    - Help women to feel less vulnerable
    - Provide relevant coping strategies

1. Avis. JAMA Intern Med. 2015;175:531. 2. Hoga. JBI Database System Rev Implement Rep. 2015;13:250.
3. Kabir. PLoS ONE 2023;18:e0289322.

Menopause and Sleep

- Women transitioning into menopause typically complain of
  - Poor sleep quality
  - Insufficient sleep
  - Nocturnal awakenings
  - Apnea
- Sleep deprivation is a known factor for
  - Cardiovascular disease
  - Diabetes
  - Obesity
  - Neurobehavioral dysfunction

Self-reported in 40% to 56% of women compared to premenopausal women

Gava G, et al. *Medicina*. 2019;55(10):688.

Apart from being disruptive and bothersome, VMS independently have adverse health consequences

- Associated with cardiovascular and metabolic changes
- Increased carotid intima thickness
- Increased carotid and aortic calcifications
- Worsening lipid profiles
- Increased insulin resistance
- Increased risk of hypertension
- White matter changes in the brain
- Linked to decreased bone mineral density and increased fracture incidenc

Non FDA approved Non hormone Treatment for VMS Due to Menopause

The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society

Recommended:

- Cognitive-behavioral therapy Clinical hypnosis
- SSRIs/SNRIs/Gabapentin***
- NK3 Fezolinetant (Level I)***
- Oxybutynin (Levels I-II)
- Weight loss
- Stellate ganglion block (Levels II-III)

*** FDA approved 7.5 mg/d paroxetine salt
*** FDA approved Fezolinetant

Not recommended due to lack of RCT efficacy data:

Paced respiration; Supplements/herbal remedies, Cooling techniques, avoiding triggers, Exercise, yoga, mindfulness-based intervention, relaxation, suvorexant, Soy foods and soy extracts, soy metabolite equol, cannabinoids, Acupuncture, calibration of neural oscillations; chiropractic interventions, clonidine; dietary modification and pregabalin)

The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society Menopause. 2023 Jun 1;30(6):573-590.

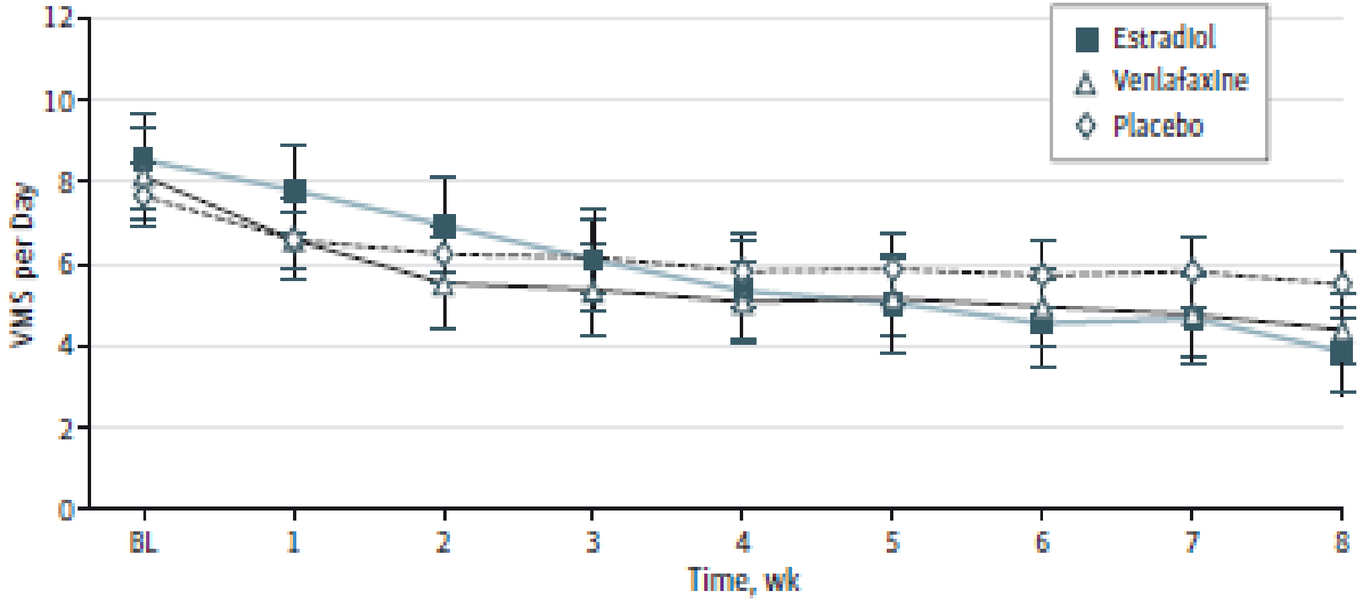
Nonhormone Pharmacologic Therapies before Neurokinin Antagonists

Medication name	Drug class	Suggested dosing	Side effects	Additional considerations
Gabapentin	Gamma-aminobutyric acid (GABA) analogue	100–300 mg-600 mg at night or adding a dose in day; Optimally at night	Dizziness, fatigue	Consider in concomitant migraine or sleep disorders
Paroxetine Escitalopram	SSRI	Paroxetine mesylate: 7.5 mg/day *** Paroxetine HCl: 10–20 mg/day Escitalopram 10-20 mg/d	Nausea, dizziness	** First US FDA-approved nonhormone option. CYP2D6 inhibition; avoid in tamoxifen users; consider in concomitant mood disorders
Venlafaxine	SNRI	37.5–150 mg/day	Nausea, dizziness	May be safer in tamoxifen users
Oxybutynin	Anticholinergic, antimuscarinic	2.5 mg–5 mg/2x daily up to 15 mg/day	Dry mouth, urinary difficulties	Avoid in elderly; may benefit concomitant overactive bladder with VMS; side effects appear dose-dependent
Clonidine-uncommonly used	Antihypertensive; α-2 adrenergic agonist	0.05–0.1 5 mg/day	Blood pressure, drowsiness, dry mouth	Inconsistent data; less effective than SSRIs/SNRIs and gabapentinoids; significant side effects

- ***First FDA approved nonhormone was 7.5 mg/d paroxetine salt
- Khan SI, et al. Int J Womens Health. 2023;15:273-287.; David et al and Sahni et al

Venlafaxine 75mg equivalent to 0.25mg estradiol for VMS

Figure 2. Frequency of Vasomotor Symptoms (VMS) by Treatment Group



Estradiol, No.	97	94	92	92	91	90	92	93	91
Venlafaxine, No.	96	91	92	92	93	91	91	89	89
Placebo, No.	146	133	136	139	139	141	138	137	137

BL Indicates baseline.

Stellate ganglion- block Sympathetic nerves

Relieve sympathetic-mediated pain & improve vasomotor dysfunction by blocking sympathetic ganglia

- Inject anesthetic agent to block the sympathetic nervous chain (sweating, flushing, via lower cervical or upper thoracic approach in upper body. 10 mL 0.5% bupivacaine Injected bilaterally under imaging guidance to front of neck, near C7 vertebra, into stellate ganglion

Reduced moderate to severe VMS in some studies- Reduced perceived and physiologically documented VMS with and without breast cancer- most recent RCT of 40 PM women, followed 12 weeks, 35 completed, 10% AE

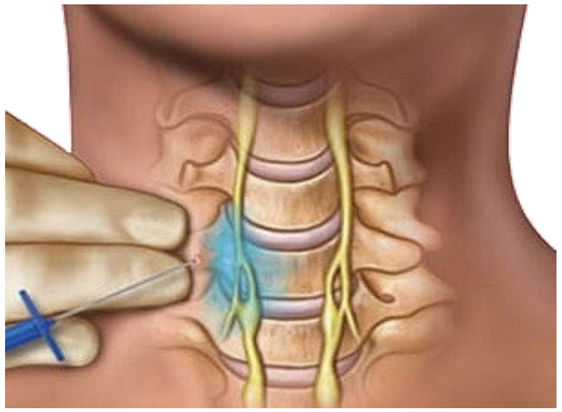
Documented effects up to 6 months

Larger trials of longer durations for effectiveness and safety are needed

Rapid onset 6-8 hrs.- immediate effects- ptosis, pupil constriction, lack of sweating, congestion, hoarseness, numbness

Requires skilled operator

- Potential serious adverse events- puncture of artery, vein, thyroid, nerve, trachea
- Requires post-procedure observation
- Unpredictable degree and duration of response; Expensive



Li Y, et al, Effects of stellate ganglion block on perimenopausal hot flashes: a randomized controlled trial. Front Endocrinol (Lausanne). 2023 Nov 28;14:1293358.

Oxybutynin- Approved for Urinary issues- used off label for VMS

- Anticholinergic FDA approved for management of urinary urge incontinence and overactive bladder.
- *MOA* Blocks sympathetic neurons that are cholinergic such as those innervating the salivary and sweat glands
- Shown to reduce moderate to severe VMS in a number of studies[15].
- *Dosages* vary 2.5mg-5mg twice daily, up to 15 mg ER daily.
- *Side effects*- Xerostomia -dry eyes or mouth, confusion, less common urinary retention,
- *Metabolized* in the liver by the P450 enzyme pathway (CYP 3A4) active via CYP3A4
- • Higher than normal plasma concentrations when taken with a CYP3A4 inhibitor- st john's wort, grapefruit juice
- *Crosses the blood brain barrier –Caution* in the elderly, due to the risk of cognitive decline
  - Patients over 65 yr, baseline cognitive impairment, or at risk for neurocognitive issues
- *Contraindicated* in narrow angle glaucoma

Cognitive behavioral therapy (CBT) Hypnosis

- **Mechanism of Action:** Cognitive reframing of symptomatology - better coping and control over VMS
- Cognitive behavioral therapy – improves sleep, mood and bother of VMS
  - some studies to reduce the frequency of VMS
- VMS rated less problematic, less interference, frequency, bother- small to mod effects
  - Duration: sustained but declines over time; stronger for natural VMS than treatment induced HF

Intervention components (Janet Carpenter TMS October 2025)

- Psychoeducation
- VMS physiology
- How thoughts and emotions affect symptom perception
- Training in relaxation and paced breathing
- Cognitive-behavioral strategies to manage VMS
- Identifying and altering triggers
- Identifying and altering negative thoughts

Muñiz V et al. Clinical Hypnosis and Cognitive Behavioral Therapy for Hot Flashes: A Scoping Review. Womens Health Rep (New Rochelle). 2025 Jan 8;6(1):1-20; Ye M et al. Efficacy of cognitive therapy and behavior therapy for menopausal symptoms: a systematic review and meta-analysis. Psychol Med. 2022 Feb;52(3):433-445.

Hypnosis

- Research-Hypnosis shown to reduce VMS of severity and frequency, and useful for reducing anxiety and improving sleep
- Comparative scoping review of 23 studies of hypnosis vs CBT, only hypnosis found significant reductions in frequency and severity of hot flashes;
- **Mechanism-** Reduces sympathetic activation & engages parasympathetic system; Deep relaxation and post-hypnotic suggestions; May alter hypothalamic thermoregulation
- **Intervention components**
  - Practice entering a deeply relaxed state
  - Individualized mental imagery
  - Suggestions of cooling

The 2023 nonhormone therapy PS of The North American Menopause Society. Menopause. 2023 Jun 1;30(6):573-590; Muñiz V et al. Clinical Hypnosis and Cognitive Behavioral Therapy for Hot Flashes: A Scoping Review. Womens Health Rep (New Rochelle). 2025 Jan 8;6(1):1-20; Elkins GR, Fisher WI, Johnson AK, Carpenter JS, Keith TZ. Clinical hypnosis in the treatment of postmenopausal hot flashes: RCT. Menopause. 2013 Mar;20(3):291-8

Weight Loss for VMS- needs more evidence

- **MOA:** Adiposity risk factor for VMS -thermoregulatory role of body fat, with adipose tissue insulating against the putative heat dissipating action of hot flashes
- Pilot trials successful; need larger, longer duration RCT trials
- *Recommended* to reduce VMS : **ideally 10 pounds or 10%of body weight**
- *Evia app* targets VMS and insomnia- evidence-based digital therapeutic that combines cooling mental imagery, relaxation, and hypnotherapy techniques to help you manage hot flashes & night sweats
- Potential application for GLP-1 inhibitors- reduce visceral fat deposits, restore insulin sensitivity and inhibit inflammatory mediator release.
- Maintaining behavioral change difficult
- Time consuming and slow process for modest benefit;
- Costs of GLP-1 inhibitors

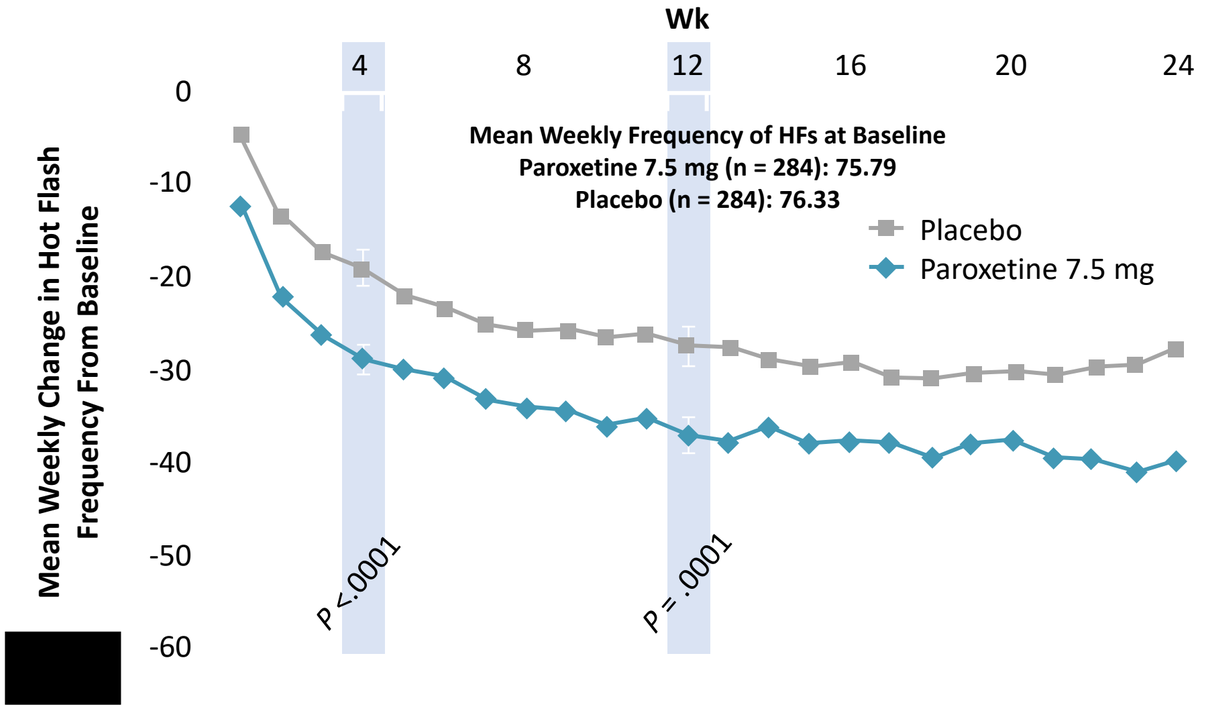
Janet Carpenter TMS October 2025; Kroenke CH, Caan BJ, Stefanick ML, Anderson G, Brzyski R, Johnson KC, LeBlanc E, Lee C, La Croix AZ, Park HL, Sims ST, Vitolins M, Wallace R. Effects of a dietary intervention and weight change on vms in the WHI. Menopause. 2012 Sep;19(9):980-8
Thurston RC, Ewing LJ, Low CA, Christie AJ, Levine MD. Behavioral weight loss for the management of menopausal hot flashes: a pilot study. Menopause. 2015 Jan;22(1):59-65;Gold EB, Crawford SL, Shelton JF, Tepper PG, Crandall CJ, Greendale GA, Matthews KA, Thurston RC, Avis NE. Longitudinal analysis of changes in weight and waist circumference in relation to incident vasomotor symptoms: SWAN Menopause. 2017 Jan;24(1):9-26.;
Kapoor E, Collazo-Clavell ML, Faubion SS. Weight Gain in Women at Midlife: A Concise Review of the Pathophysiology and Strategies for Management. Mayo Clin Proc. 2017 Oct;92(10):1552-1558

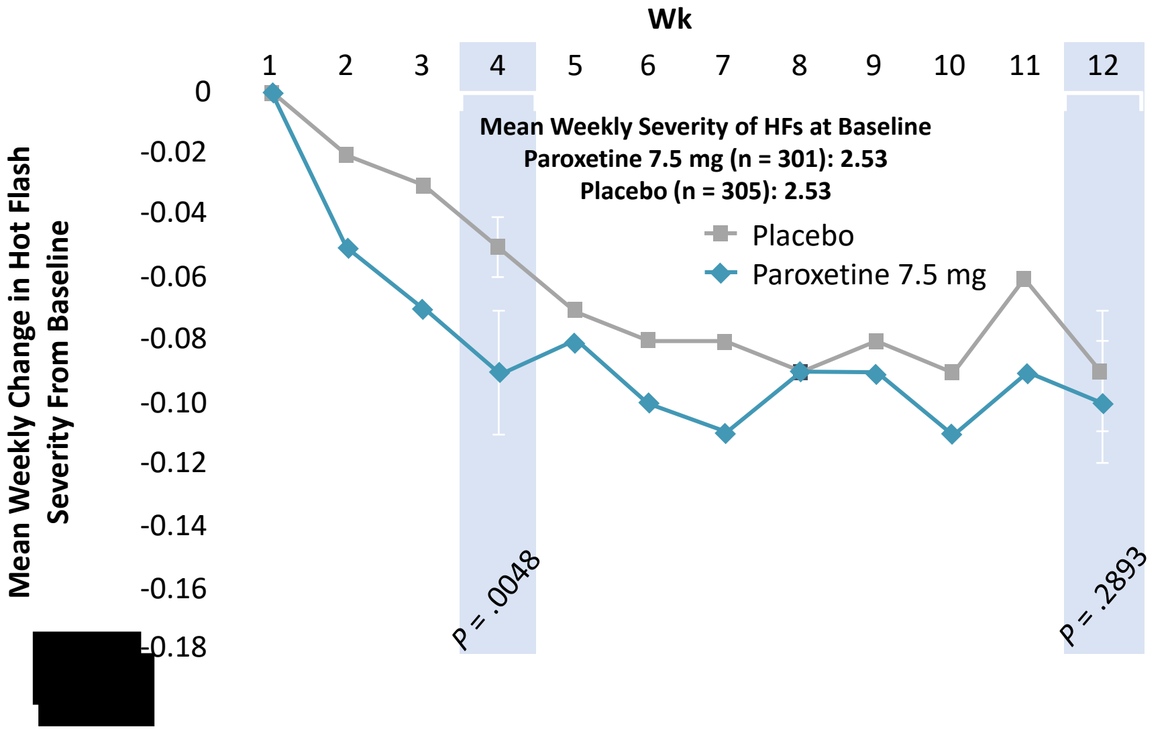
FDA approved Non hormone Treatment for VMS Due to Menopause

VERTIS CV

Low-Dose Paroxetine for VMS FDA approved for VMS

- Paroxetine salt 7.5 mg/day evaluated in postmenopausal women





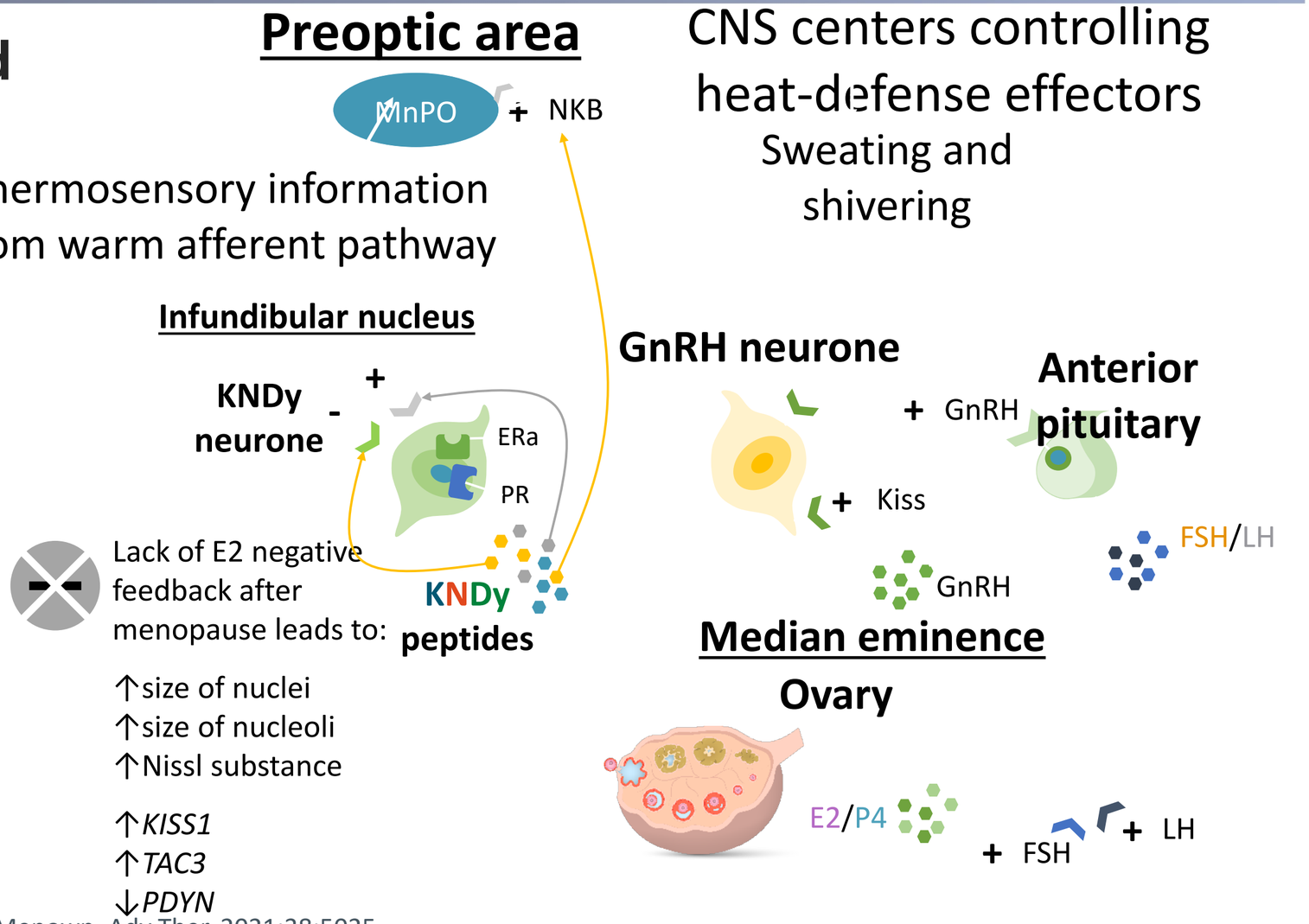
- Most treatment-emergent AEs were mild or moderate
- AEs occurring ≥2% of treatment group and at double frequency compared with placebo group: nausea (3.8 vs 1.4%), fatigue (3.4 vs 1.5%), and dizziness (2.0 vs 0.8%)

Simon. Menopause. 2013;20:1027.

Thermoregulation

Hypothalamus

- **During menopause, decreased estrogen leads to**
  - **Overstimulation of KNDy neurons**
  - **Increased NKB neurotransmitters**
  - **Increased activity in thermoregulatory center**
  - **Hypersensitivity to external cues from peripheral sensors**
  - **Triggering of heat dissipation effectors**

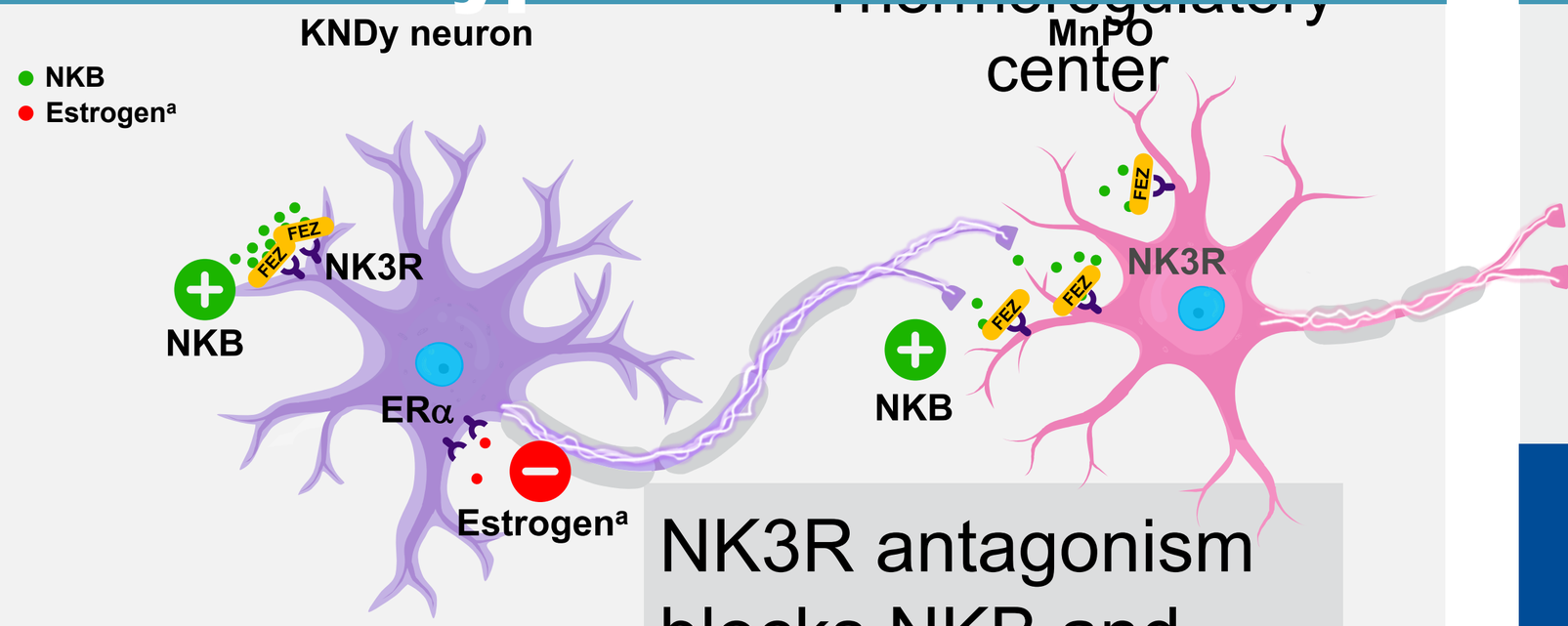


Koysombat. Best Pract Res Clin Endocrinol Metab. 2024;38:101774. Menown. Adv Ther. 2021;38;5025.

New and Emerging Pharmacotherapeutic Options to Better Manage VMS due to Menopause

Fezolinetant moderates neuronal activity to treat VMS

Hypothalamus



NK3R antagonism blocks NKB and moderates neuronal activity

Periphery

Treatment of VMS

↓ VMS Frequency and Severity

Fezolinetant is a selective NK3R antagonist that blocks NKB binding on the KNDy neuron to moderate neuronal activity in the thermoregulatory center, **helping to restore thermoregulatory balance**[1-5]

Neurokinin Receptor Antagonists

- Specialized hypothalamic KNDy neurons utilize NKB signaling on NK3R. Through NK3R antagonism, the signaling pathway can be disrupted and potentially attenuate VMS

	Fezolinetant	Elinzanetant
	FDA approved 5/2023	FDA approved 10/2025
Class	NK3 antagonist	Dual NK1,3 antagonist
MoA	Blocks NKB receptor on the KNDy neuron, working to modulate activity in the thermoregulatory center	Blocks NKB and substance P on reproductive axis
Dose	45 mg orally at bedtime Follow LFTs	120 mg orally daily

- Fezolinetant PI; Pinkerton. Menopause. 2024;[Epub].

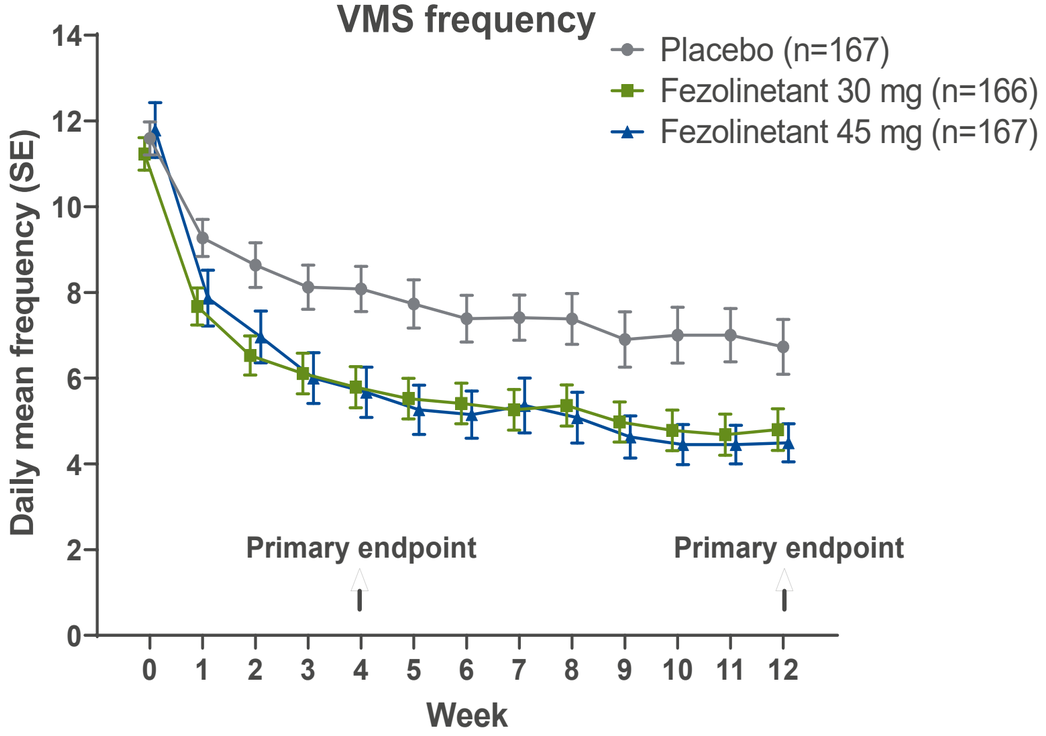
Neurokinin Receptor Antagonists Fezolinetant

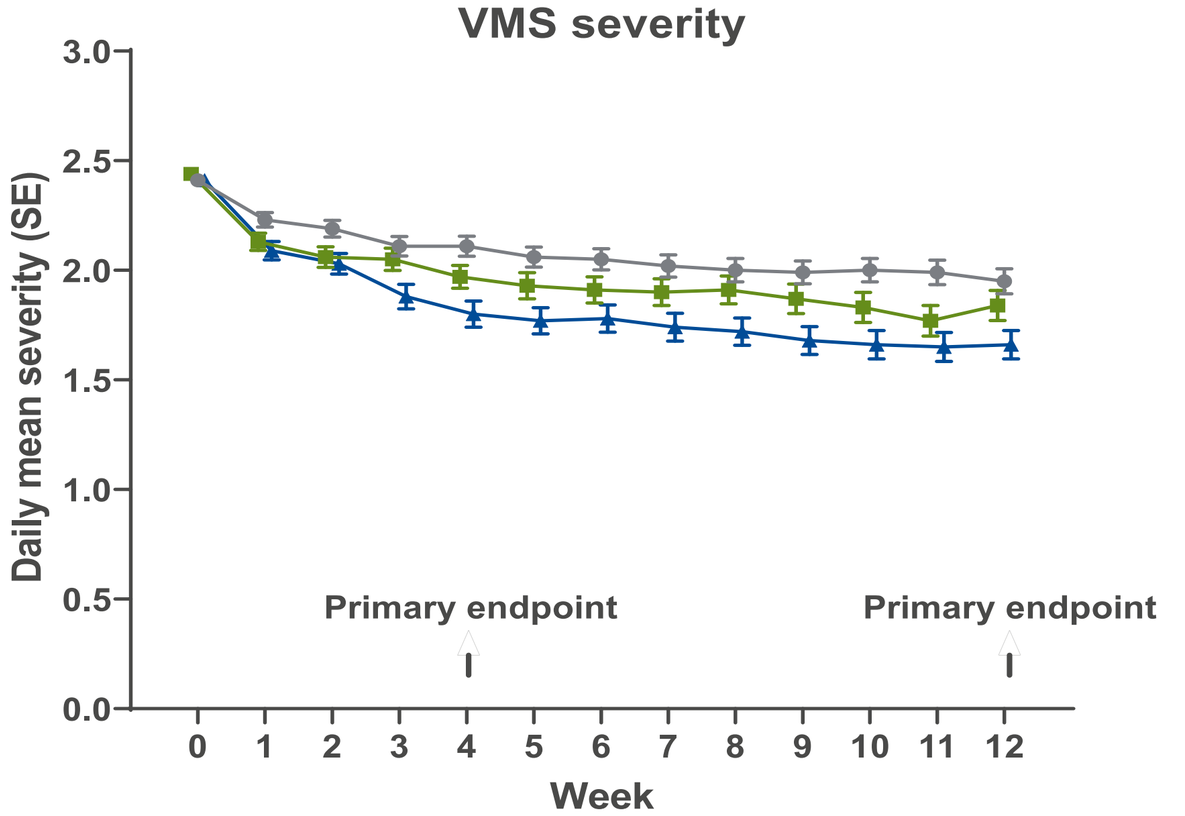
- Fezolinetant NK3R- 45 mg oral daily
- First neurokinin receptor antagonist to receive FDA approval for VMS of menopause
  - Reduced frequency of VMS about 65%, significantly > placebo, similar to the 75% reduction seen with hormone therapy
  - Efficacy evident within one week
  - Appears to have very good safety profile including endometrial safety
  - **Baseline LFTs, monthly for 3 months and every 3 months for 9 months**
- Contraindicated with CYP1A2 inhibitors-Fluvoxamine, Ciprofloxacin, mexiletine
- Comprehensive analysis of clinical data, regulatory assessments, and epidemiological literature does not support an increased risk of neoplasms.
- Phase 3 RCT in progress for women with breast cancer on hormone therapies Clinicaltrials.gov NCT06440967

Lederman S,et al Fezolinetant for treatment of moderate-to-severe VMS associated with menopause (SKYLIGHT 1): a phase 3 RCT. Lancet. 2023 Apr 1;401(10382):1091-1102; Johnson KA Efficacy and Safety of Fezolinetant in Moderate to Severe VMS with Menopause: A Phase 3 RCT. J Clin Endocrinol Metab. 2023 Jul 14;108(8):1981-1997;Neal-Perry G, et al. Safety of Fezolinetant for Vasomotor Symptoms Associated With Menopause: A RCTl. Obstet Gynecol. 2023 Apr 1;141(4):737-747;Morga A, eta l. Systematic review and network meta-analysis comparing the efficacy of fezolinetant with hormone and nonhormone therapies for treatment of VMS due to menopause. Menopause. 2024 Jan 1;31(1):68-76;.

Fezolinetant reduced VMS frequency and severity across the 12-week period (skylight 2) NK3 to 52 wk

Percentage reduction in frequency of moderate and severe VMS per 24 hours by week (FAS)





Mean (A) frequency and (B) severity of moderate and severe VMS during

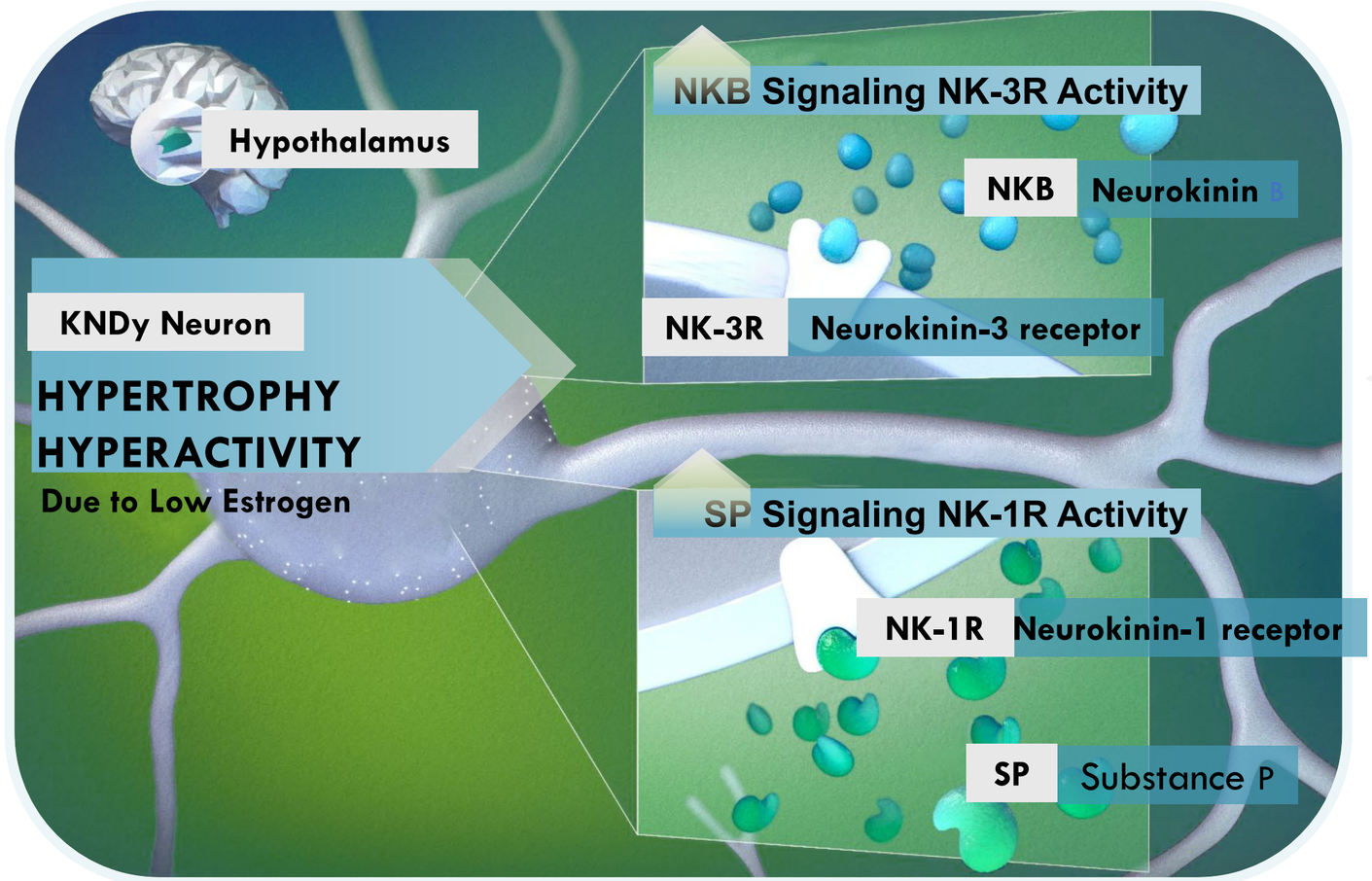
Both fezolinetant doses statistically significantly reduced VMS frequency and severity at weeks 4 and 12 vs placebo.

Johnson KA, Martin N, Nappi RE,et al… Santoro N. Efficacy and Safety of Fezolinetant in Moderate to Severe Vasomotor Symptoms Associated With Menopause : A Phase 3 RCT. J Clin Endocrinol Metab. 2023 Jul 14;108(8):1981-1997.

Who to consider for the use of fezolinetant?

- Moderate to severe hot flashes and night sweats
  - Estrogen sensitive breast or uterine cancers
  - VTE, stroke, migraine with aura
- Normal baseline liver function tests
- Need to monitor LFTs every 3 months for first 9 months- in clinical trial no persistent elevated LFTs after stopping
- 1-2% reported AE-headaches, abdominal pain, diarrhea, insomnia, back pain, hot flushes, and reversible elevated hepatic transaminases.[4,5] Serious adverse events infrequent
- Effective diverse populations, white or black race, BMI of 30 kg/m2 or higher, younger or older than age 55, smokers, former smokers, and never smokers, in US as well as in Europe
- Concomitant use of moderate CYP1A2 inhibitors, including many antidepressants and cimetidine, should be avoided.
- Estrogen sensitive breast or uterine cancers

Theory of Vasomotor Symptoms NK-3, NK1



KNDy, estrogen-sensitive kisspeptin/neurokinin B/dynorphin; NKB, neurokinin B; NK-1R, neurokinin-1 receptor; NK-3R, neurokinin-3 receptor; SP, substance P.

1. Rance NE, et al. Front Neuroendocrinol 2013;34(3):211–27; 2. Ratti E, et al. Sleep 2013;36(12):1823–30.
2. EFFECT OF ELINZANETANT FOR THE TREATMENT OF VASOMOTOR SYMPTOMS ASSOCIATED WITH MENOPAUSE: POOLED DATA FROM TWO PHASE 3 STUDIES Presented at TMS October 2025

KNDy neurons, located in the **hypothalamus**, are thought to play a **key role in thermoregulation and sleep**

Declining estrogen levels during and after the menopause transition lead to hypertrophy and hyperactivity of KNDy neurons, accompanied by elevated gene expression of neurotransmitters including neurokinin (NK) B and substance P (SP)[1]

Hyperactivation of KNDy neurons has been related to disruption of thermoregulation which may trigger hot flashes[1]

Substance P and NK-1R may play a role in primary insomnia[2]

Elinzanetant dual NK1, 3 Neurokinin receptor antagonist for VMS

- First dual neurokinin-1,3 (NK-1,3) receptor antagonist- working through neurokinin receptor NK3 for VMS and substance P from NK1 for sleep and mood effects
- RCTs OASIS 1, 2, 3 Elinzanetant a daily 120 mg shown to reduce the frequency and severity of moderate to severe VMS, rapidly within one week,4 and 12 weeks, with improved menopause related QOL and reduced sleep disturbance at 26 weeks, and over 52 weeks.
- *Side effects*- headache, fatigue , arthralgia, CNS. Don't take if pregnant
- No liver toxicity, no concerns endometrial or breast cancer; LFTs baseline& 3 m
- Metabolized CYP 3A4- avoid cyclosporine, fentanyl, tacrolimus and grapefruit juice
- *Tested in Breast cancer*-52 Week OASIS 4 RCT-
  - Similar efficacy and safety in women on endocrine therapy for breast cancer-tamoxifen and aromatase inhibitors NEJM 2025

Pinkerton JV, Simon JA, Joffe H, et al. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 RCT. JAMA. 2024 Aug 22:e2414618. Panay N, Joffe H, Maki PM, et al Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: A Phase 3 RCT. JAMA Intern Med. 2025 Sep 8:e254421. doi: 10.1001/jamainternmed.2025.4421. Epub ahead of print; Cardoso F, Parke S, Brennan D J. Elinzanetant for Vasomotor Symptoms from Endocrine Therapy for Breast Cancer. N Engl J Med. 2025 Aug 21;393(8):753-763.

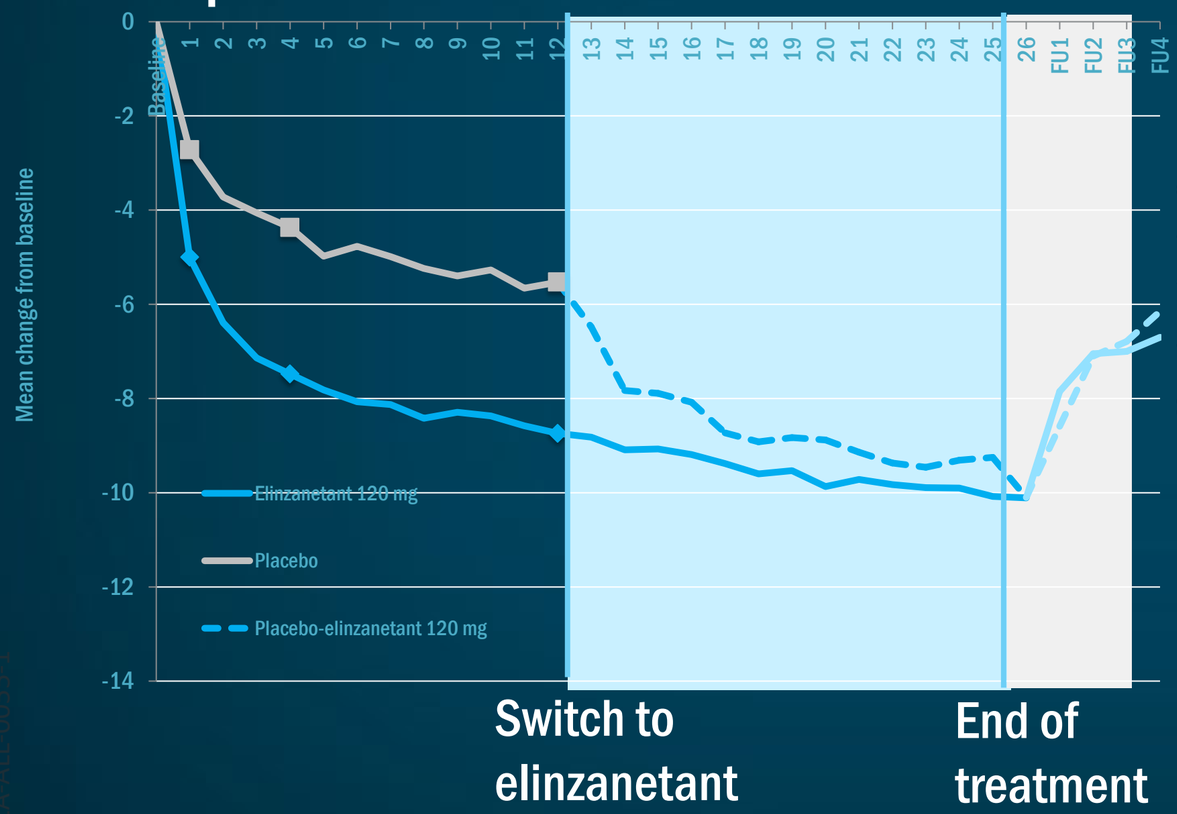
Mean change from baseline in frequency of moderate/severe VMS over time

OASIS 1

Double-blind phase

Elinzanetant phase

Follow up



Switch to elinzanetant

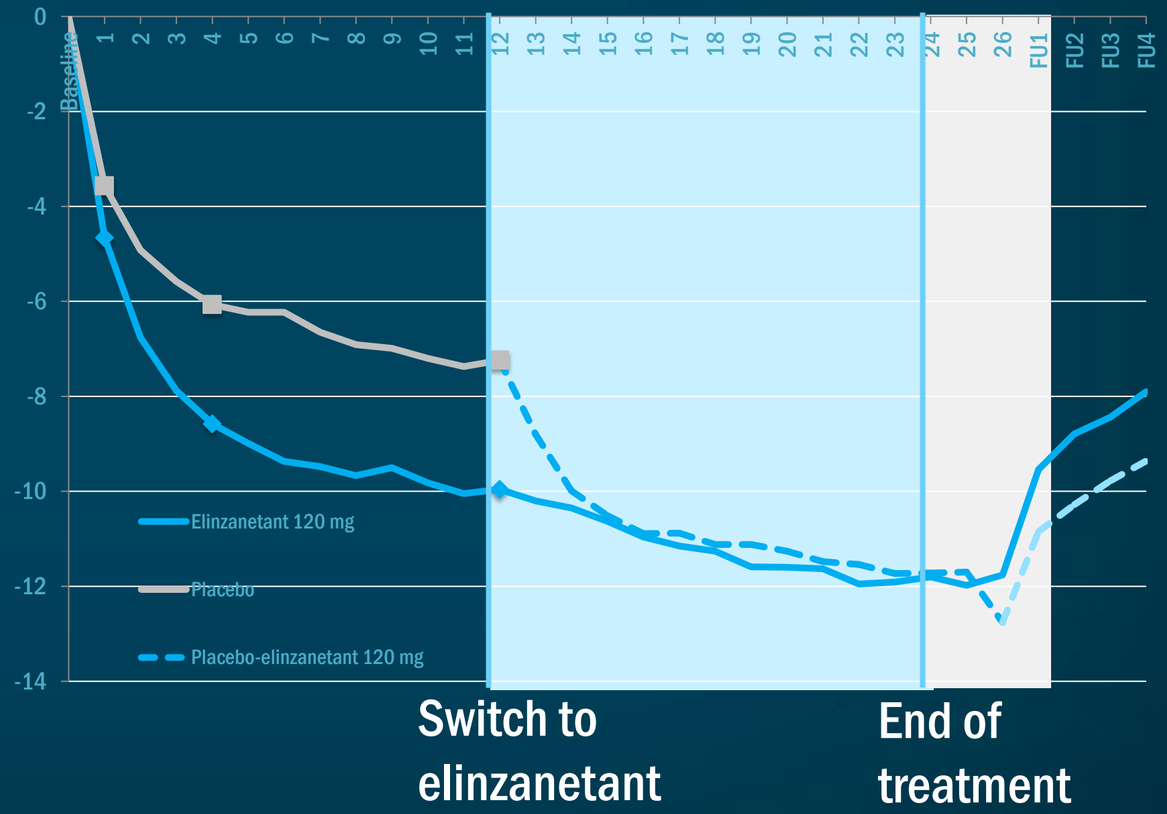
End of treatment

OASIS 2

Double-blind phase

Elinzanetant phase

Follow up



Switch to elinzanetant

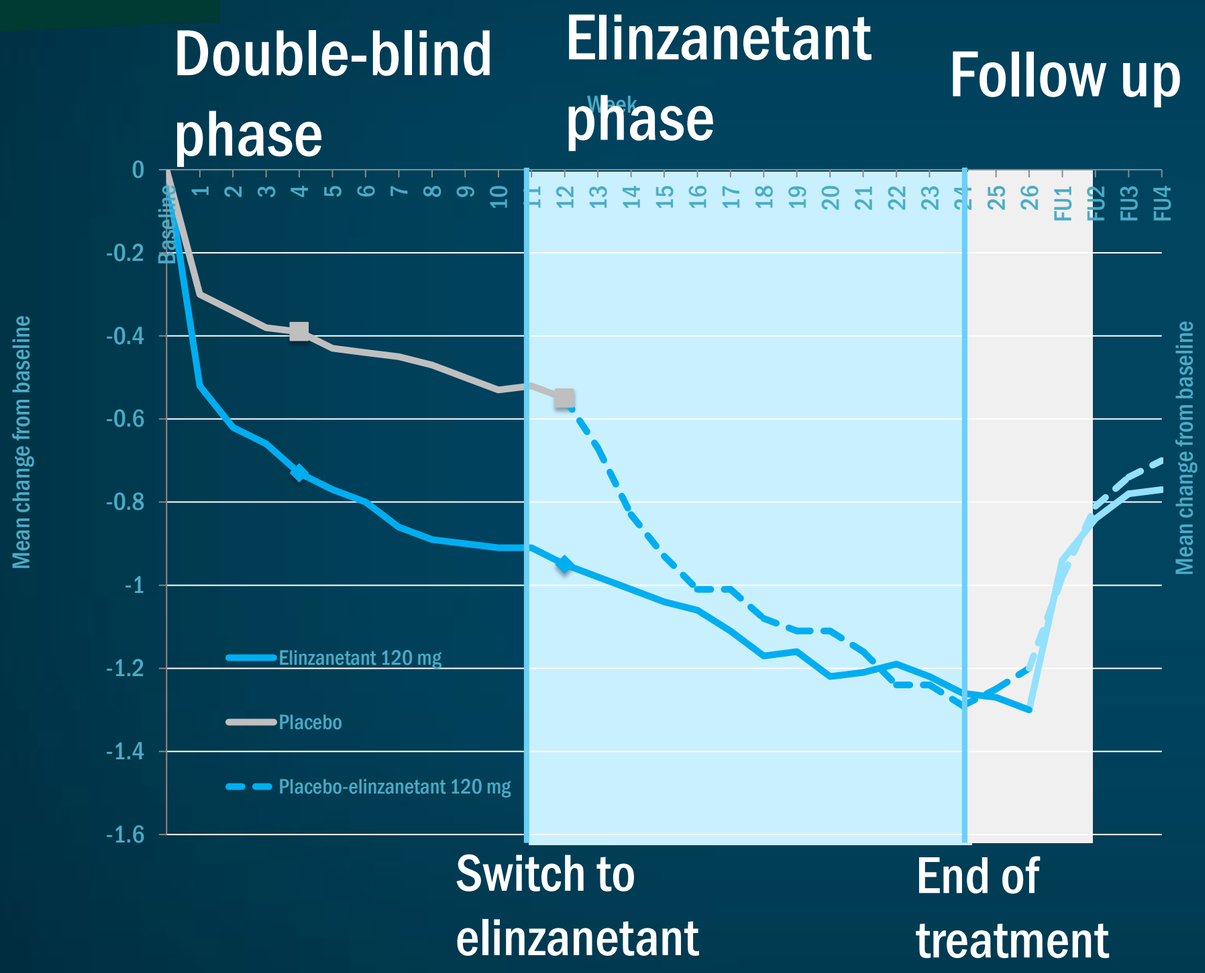
End of treatment

Simon, et al. OASIS 1 poster presented at ACOG, 2024. VMS, vasomotor symptoms.
Pinkerton, et al. OASIS 2 poster presented at ACOG, 2024.

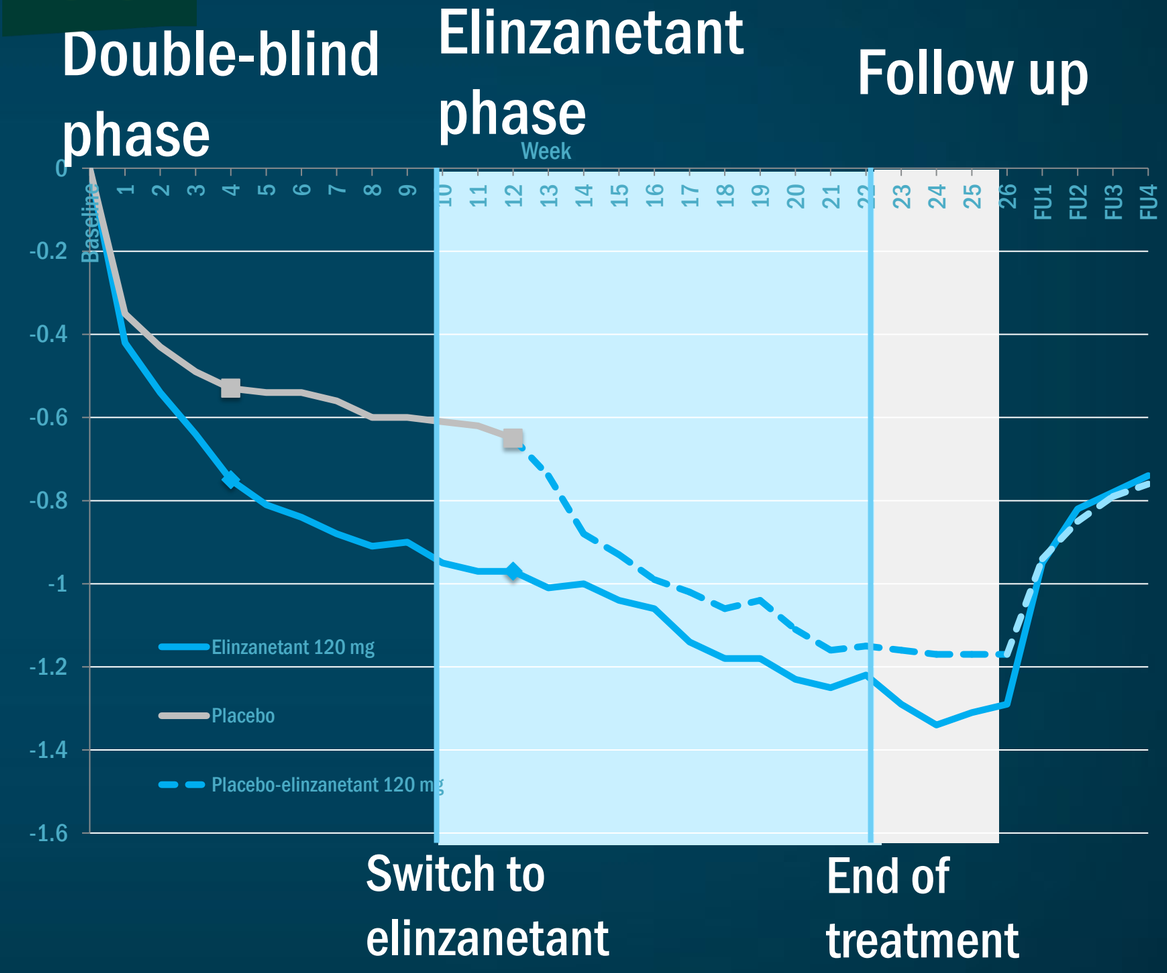
Pinkerton JV, Simon JA, Joffe H, et al. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 Randomized Clinical Trials. JAMA. 2024 Aug 22:e2414618.

Mean change from baseline in severity of VMS over time

OASIS 1



OASIS 2



Simon, et al. OASIS 1 poster presented at ACOG, 2024 VMS, vasomotor symptoms
Pinkerton, et al. OASIS 2 poster presented at ACOG, 2024
Pinkerton JV, Simon JA, Joffe H, et al. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 Randomized Clinical Trials. JAMA. 2024 Aug 22:e2414618

Most frequent TEAEs: OASIS 1 and 2

N (%) OASIS 1	Elinzanetant 120 mg week 1-12 (N=199)	Placebo week 1-12 (N=194)	Elinzanetant 120 mg week 13-26 (N=171)	Placebo-elinzanetant 120 mg week 13-26 (N=168)	Elinzanetant week 1-26 (N=367)
Headache	14 (7.0%)	5 (2.6%)	4 (2.3%)	6 (3.6%)	24 (6.5%)
Fatigue	14 (7.0%)	3 (1.5%)	0	1 (0.6%)	15 (4.1%)
Arthralgia	10 (5.0%)	10 (5.2%)	1 (0.6%)	1 (0.6%)	12 (3.3%)

N (%) OASIS 2	Elinzanetant 120 mg week 1-12 (N=201)	Placebo week 1-12 (N=199)	Elinzanetant 120 mg week 13-26 (N=171)	Placebo-elinzanetant 120 mg week 13-26 (N=180)	Elinzanetant 120 mg week 1-26 (N=381)
Headache	18 (9.0%)	5 (2.5%)	4 (2.3%)	4 (2.2%)	24 (6.3%)
Fatigue	11 (5.5%)	3 (1.5%)	1 (0.6%)	3 (1.7%)	15 (3.9%)

Simon, et al. OASIS 1 poster presented at ACOG, 2024. Pinkerton, et al. OASIS 2 poster presented at ACOG, 2024.

Pinkerton JV, Simon JA, Joffe H, et al. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 Randomized Clinical Trials. JAMA. 2024 Aug 22:e2414618

OASIS 3 52 Week Study of Elinzanetant Efficacy

Elinzanetant showed favorable efficacy and safety for treatment of moderate-to-severe VMS associated with menopause

Significant reductions from baseline to week 12 in moderate-to-severe VMS frequency were shown with elinzanetant versus placebo; reductions maintained throughout study duration

Improvements in measures of sleep disturbances and menopause-related quality of life with elinzanetant over 52 weeks, based on descriptive analyses

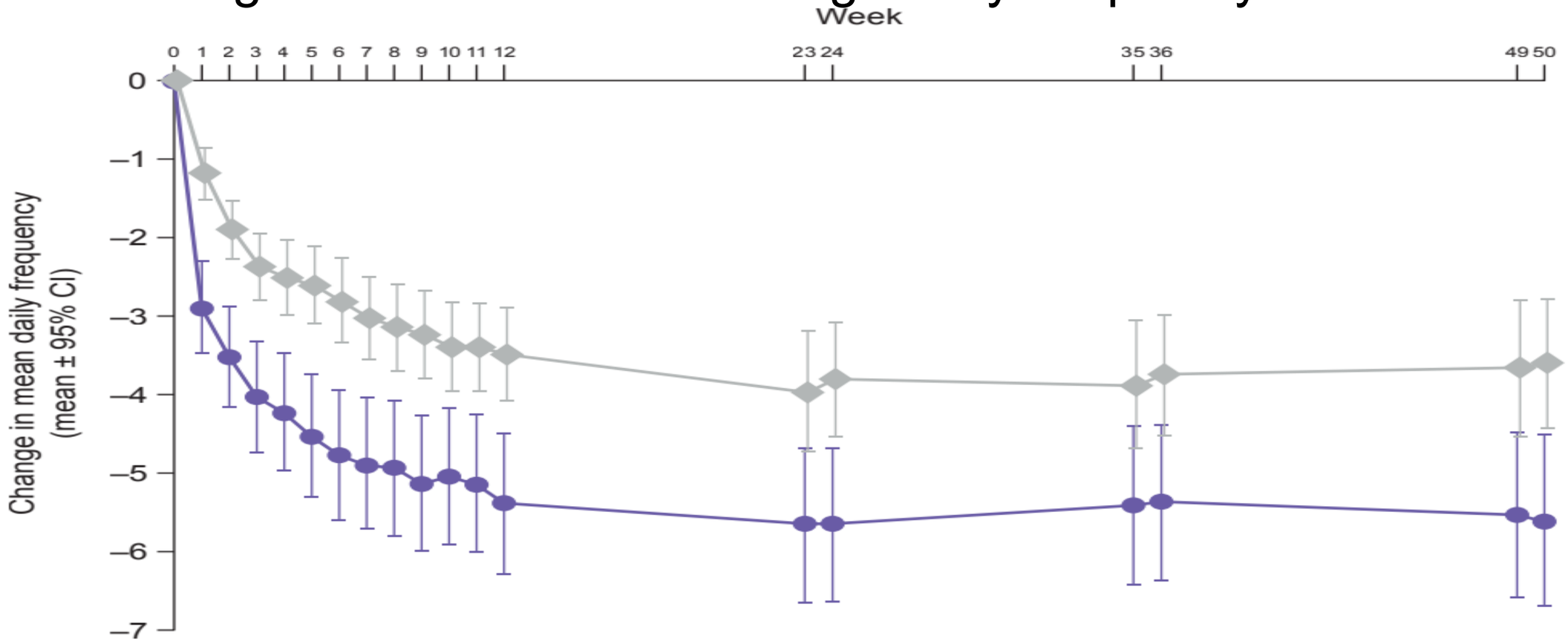
OASIS 3 supported the results of OASIS 1 and 2, demonstrating efficacy over a longer study duration and in a population with a VMS profile representative of clinical practice

Panay N, Joffe H, Maki PM, et al Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: A Phase 3 Randomized Clinical Trial. JAMA Intern Med. 2025 Sep 8:e254421. doi: 10.1001/jamainternmed.2025.4421. Epub ahead of print.

Efficacy and Long-Term Safety of Elinzanetant for the Treatment of VMS Associated with Menopause: A Phase 3 Randomized Trial (OASIS 3) over 52 we

628 PM women 83 sites, 9 countries

Mean change from baseline in average daily frequency of moderate-to-severe V



- Panay N, Joffe H, Maki PAithal GP, et al. Clin Pharmacol Ther 2011;89:806–15; 2. Finkelstein JS, et al. J Clin Endocrinol Metab 2008;93:861–8; 3. Pinkerton JV, et al. JAMA 2024. doi:10.1001/jama.2024.14618 Abstract 2024 Menopause Society meeting being held in Chicago, Illinois 9-14-2024

OASIS 4- 474 PM women – 90 centers 16 countries, not in US

over 52 weeks and optionally for an additional 2 years

- Phase III study - treatment mod- to- severe VMS caused by **adjuvant endocrine therapy in women with breast cancer or at high risk of developing breast cancer**
  - **Tamoxifen or Aromatase Inhibitors**
- Statistically significant reductions in the frequency of mod- to- severe VMS from baseline to week 4 and 12 compared to placebo.
  - reduction at week 1 and maintained effects over the study period
- Demonstrated reductions in severity of VMS at week 4 and 12
- Improvements sleep disturbances and menopause-related QOL at week 12 compared to placebo.
- Safety profile over 52 weeks consistent with previously conducted studies

Cardoso F, Parke S, Brennan DJ. Elinzanetant for Vasomotor Symptoms from Endocrine Therapy for Breast Cancer. N Engl J Med. 2025 Aug 21;393(8):753-763

Key Learning Points

- 1. Hormone Therapy remains the most effective treatment for women with bothersome hot flashes, particularly for those under age 60 and within 10 years of menopause onset
- 2. For women who can’t or choose not to take hormone therapy, there are nonhormonal treatment options available
- FDA approved options include 7.5 mg paroxetine salt and 45 mg Fezolinetant (NK3) and Elinzanetant (NK1, NK3) receptor antagonist
- Nonhormone non FDA options shown effective in RCTs include low dose antidepressants (SSRIs,SNRIs), gabapentin, oxybutynin
- Others shown effective include stellate ganglion blocks, hypnosis, clonidine.
- Women with bothersome hot flashes should have individualized discussions with reevaluation on an annual basis or as new information becomes available.

KEY LEARNING POINTS

- For women who can’t or choose not to take hormone therapy, there are nonhormonal treatment options available- individualized discussion
- FDA-approved nonhormonal VMS options
  - Paroxetine salt (7.5 mg)
  - Neurokinin Targeted Therapies
    - Fezolinetant NK3 (45 mg),
    - Elinzanetant 120 mg
- FDA approved used off-label for VMS shown effective in RCTs
- Prescription: low dose antidepressants (SSRIs, SNRIs), gabapentin, oxybutynin,
- Others: stellate ganglion block, hypnosis, cognitive behavioral therapy, possibly weight loss, clonidine.

Thank you

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