MAYO CLINIC | School of Continuous Professional Development

19TH ANNUAL

WOMEN'S HEALTH UPDATE 2023

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NON-HORMONE MANAGEMENT OF VMS

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Associate Chair, Equity Inclusion & Diversity DOM
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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

- Proctor & Gamble, Triangle Insights Group, Everyday Health

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

Gabapentin, oxybutynin, SSRI/SNRI's

All relevant financial relationships have been mitigated.

LEARNING OBJECTIVES

- Describe briefly the menu of available non-hormonal options for vasomotor symptom treatment
- Examine a few studies related to non-hormonal treatment options, including emerging therapies
- Apply a guideline for non-hormonal options for menopause symptom treatment
    - North American Menopause Society

INDICATIONS FOR USE OF MENOPAUSAL HORMONE THERAPY (HT)

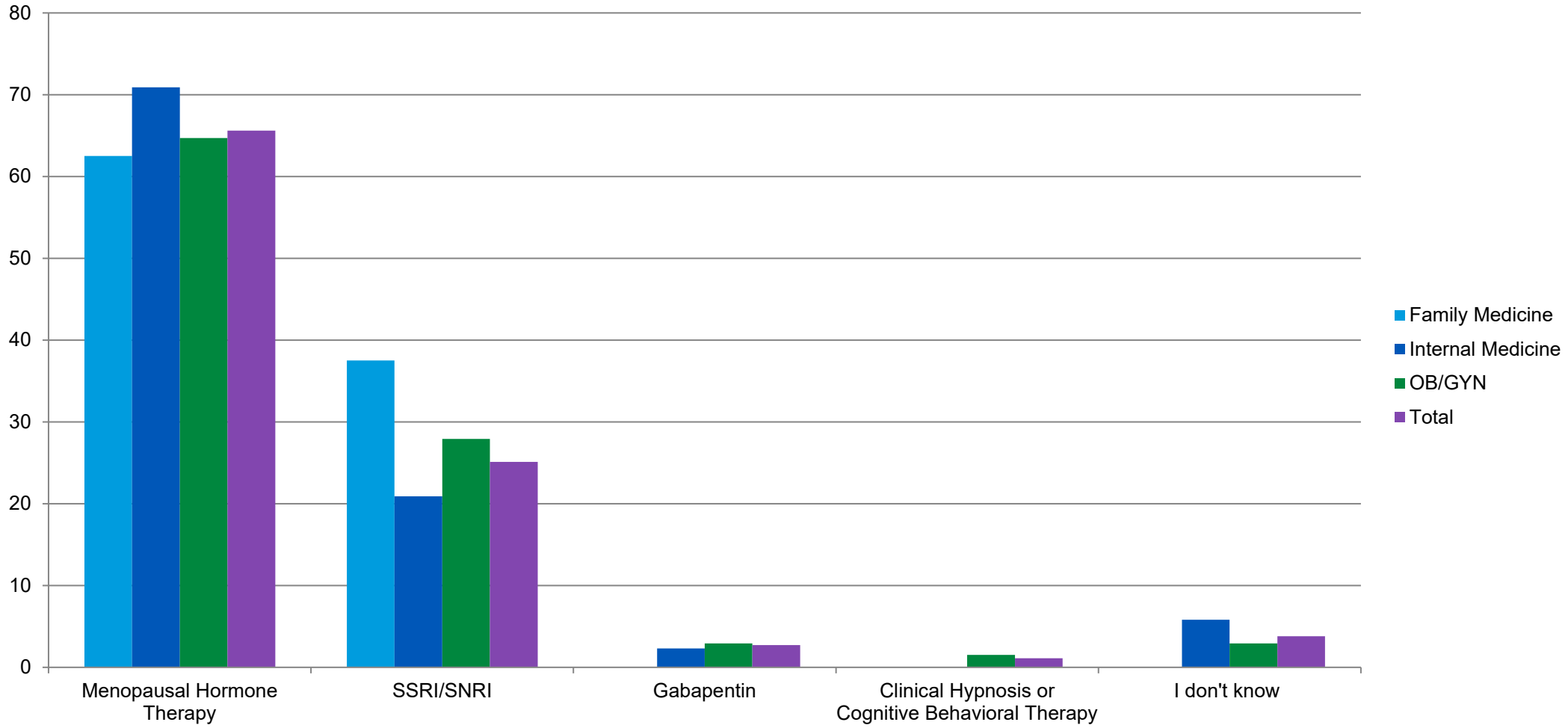
Vasomotor symptom management

- First line therapy for relief of menopause symptoms in appropriate candidates

Prevention of bone loss

NAMS 2022 position statement; Menopause 2022; 29(7)

FIRST CHOICE FOR TREATMENT FOR SEVERE VMS: 34.4% INDICATED THEY WOULD NOT OFFER HT TO A SYMPTOMATIC, NEWLY MENOPAUSAL WOMAN WITHOUT CONTRAINDICATIONS



CASE 1: ROSE IS A 49 YO CFO

- She presents with hot flashes & night sweats
- Her last menstrual cycle was 6 months ago.
- PMH: Unprovoked DVT anticoagulated for 3 months
- FH: DVT in 2 uncles, 1 cousin
- Her vitals, labs and exam are unremarkable.

Join: **vevox.app** ID: **XXX-XXX-XXX**

POLL OPEN

WHAT DO YOU OFFER HER?

1 Tell her to get a fan and tough it out

2 Prescribe paroxetine 7.5 mg nightly

3 Start estradiol 0.05 mg transdermal twice weekly and progesterone 100 mg nightly

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WHAT DO YOU OFFER HER?

- Tell her to get a fan and tough it out
- **Prescribe paroxetine 7.5 mg nightly**
- Start estradiol 0.05 mg transdermal twice weekly and progesterone 100 mg nightly

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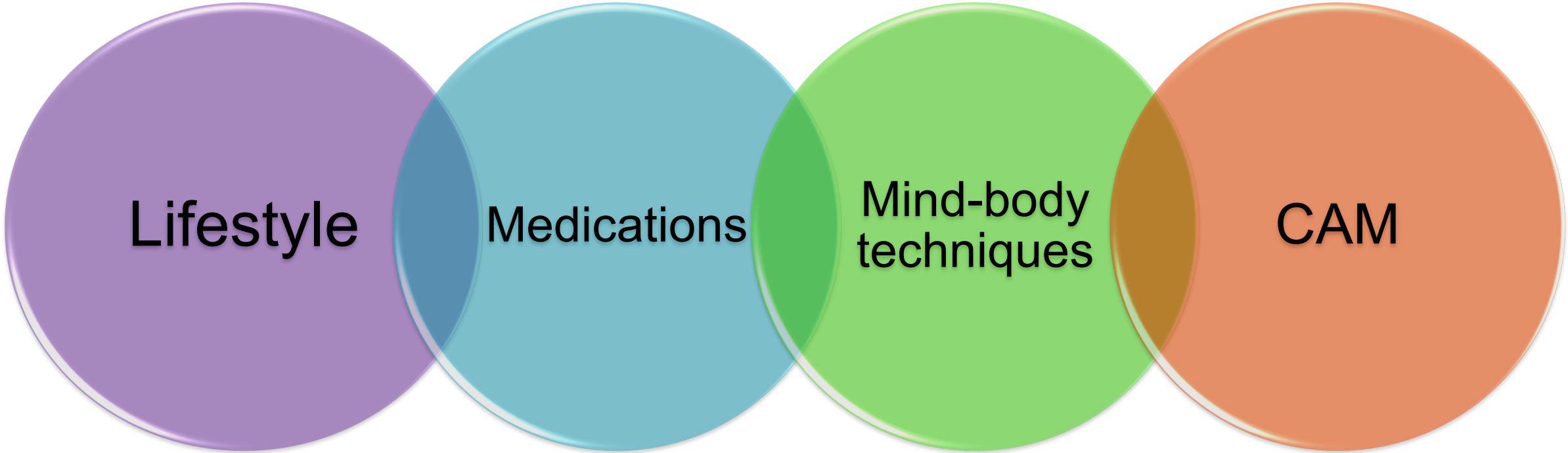
MENU OF OPTIONS



NAMS POSITION STATEMENT: 2015

NORTH AMERICAN MENOPAUSE SOCIETY 2015 NON-HORMONAL THERAPY GUIDELINES

- **Recommend**:*
  - cognitive-behavioral therapy
  - clinical hypnosis
  - paroxetine salt only FDA approved non-hormonal medication available
  - other SSRI and SNRI, gabapentinoids & clonidine show evidence of efficacy
- **Recommend with caution**: weight loss, mindfulness-based stress reduction, S-equol derivatives of soy isoflavones, and stellate ganglion block

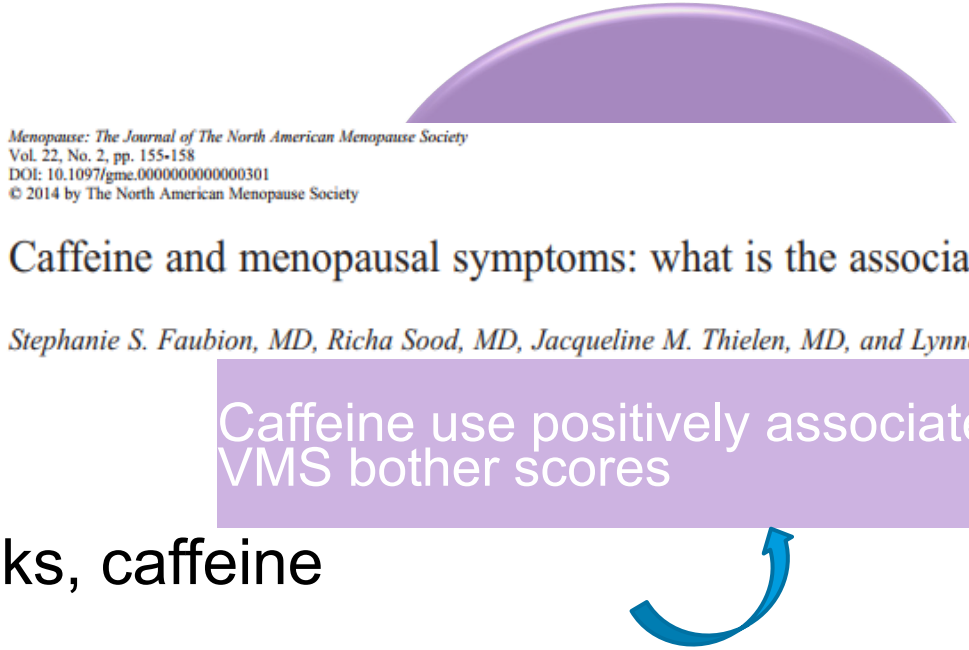
Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of the North American Menopause Society. Menopause

NAMS GUIDELINE: NOT RECOMMENDED *FOR VMS TREATMENT*

- Due to negative, insufficient, inconclusive data
  - Cooling techniques
  - Avoidance of triggers
  - Exercise
  - Yoga
  - Paced respiration
  - Relaxation
  - OTC supplements & herbal therapies
  - Acupuncture
  - Calibration of neural oscillations
  - Chiropractice interventions

MENU OF OPTIONS

- Cooling techniques
  - Clothing & environmental
- Avoid triggers
  - Alcohol, spicy foods, hot food/drinks, caffeine
- Exercise
  - Regular aerobic exercise
- Yoga
  - Lyengar, tranditional Indian, integrated, Yogasana, and Tibetan
- Weight loss



Menopause: The Journal of The North American Menopause Society
Vol. 22, No. 2, pp. 155-158
DOI: 10.1097/gme.0000000000000301
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Caffeine and menopausal symptoms: what is the association?

Stephanie S. Faubion, MD, Richa Sood, MD, Jacqueline M. Thielen, MD, and Lynne T. Shuster, MD

Caffeine use positively associated with VMS bother scores

Stuenkel et al. Endocrine Society practice guideline. J Clin Endocrinol Metab.2015;100(11):3975-4011.
NAMS 2015 position statement. Menopause.2015;126:859-876.

WEIGHT LOSS

- Adiposity protective against hot flashes?
  - Increasing body fat during menopause associated with > subsequent VMS

- Behavioral weight loss program in 40 women
  - 8.8 kg weight loss in intervention group
  - Reductions in weight and hot flashes significantly correlated
  - **Hot flash reduction was a major motivator for losing weight**

Thurston RC et al. Menopause.2015;22(1):59-65.
Ryan K et al. Kistner's Gynecology and Women's Health, 7th ed St Lewis, MO: Mosby Inc; 1999
Gold E, Colvin A, Avis N, et al. Am J Public Health 2006; 96: 1226–1235
Thurston RC, Sowers MR, Sternfeld B, et al.. Am J Epidemiol 2009; 170: 766–774

MENU OF OPTIONS

- FDA approved*
  - Paroxetine mesylate (Brisdelle)

- Off Label
  - Other SSRI's (citalopram, escitalopram)*
  - SNRI's (venlafaxine, desvenlafaxine)*
  - Gabapentinoids (gabapentin & pregabalin)*
  - Clonidine*

Nelson HD et al JAMA 2006;295(17): 2057-2071
NAMS position statement. Menopause. 2015;22(11):1155-1172.

PAROXETINE MESYLATE (BRISDELLE)

- 1st non-hormonal medication FDA approved for vasomotor symptoms
- 7.5 mg daily
- No titration necessary
- Doesn’t appear to cause weight gain or sexual adverse effects

Stearns et al. JAMA 2003; 289 (21): 2827-2834
Portman et al. Menopause.2014;21(10):1082-1090

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI'S)

- Hot flash frequency reduced by 25 to 69%
  - Sertraline and fluoxetine yielded inconsistent and statistically insignificant results
- Lower doses than used to treat psychiatric d/o
- Paroxetine:10-25 mg/day
- Escitalopram:10-20 mg/d
  - Can start with 5mg/d for older women
- Citalopram:10-20 mg/d

Freeman et al. JAMA 2011;305(3):267-274
Kalay AE Menopause 2007;14(2)223-9
Gordon et al Menopause 2006;13 (4):568-75

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRI'S)

- Venlafaxine
  - 37.5 mg x 1 week, then 75 mg/day

- Desvenlafaxine
  - 100 – 150 mg/day
  - Start 25 – 50 mg/d then titrate up

Loprinzi CL et al: Lancet 356: : 2059,2000 -2063
Sun Z et al Gynecol Obstet Invest. 2013;75(4): 255-262
Archer DF et al Amer J Obstet Gynecol 2009:200:1-10
Evans et al Obstet Gynecol 2005:105:161-6

GABAPENTINOIDS

- Gabapentin
  - Similar efficacy to estrogen at high doses
  - **Side effect**: sedation and lethargy
    - *Good for those with disruptive sleep*
  - Start with 300 mg at night (100 mg if concerned about sensitivity), then increase by 300 mg as tolerated [900-2,400 mg/day]
- Pregabalin
  - 150-300 mg/day (reduced VMS by 59 and 61% respectively)
  - Side effect: dizziness, cognitive difficulties, weight gain
  - Schedule V controlled substance (potential for abuse)
    - Not used often for VMS due to these factors

Sideras K, Loprensi CL. J Natl Compr Can Netw.2010;3(10):1171-1179
Reddy SY et al Obstet Gynecol 2006;108(1);41-48
Guttoso et al Obstet Gynecol 2003;101(2):337-345

CLONIDINE

- α-2-andrenergic receptor agonist
- Multiple RCTs show efficacy in lowering VMS
  - Less effective than SSRI/SNRIs & gabapentinoids
- 0.1 mg/day
  - Transdermal gives more stable blood levels
- **Side effects**: hypotension, bradycardia, dizziness, headache, constipation, dry mouth, rebound hypertension following cessation
  - *Due to side effects, not often used*

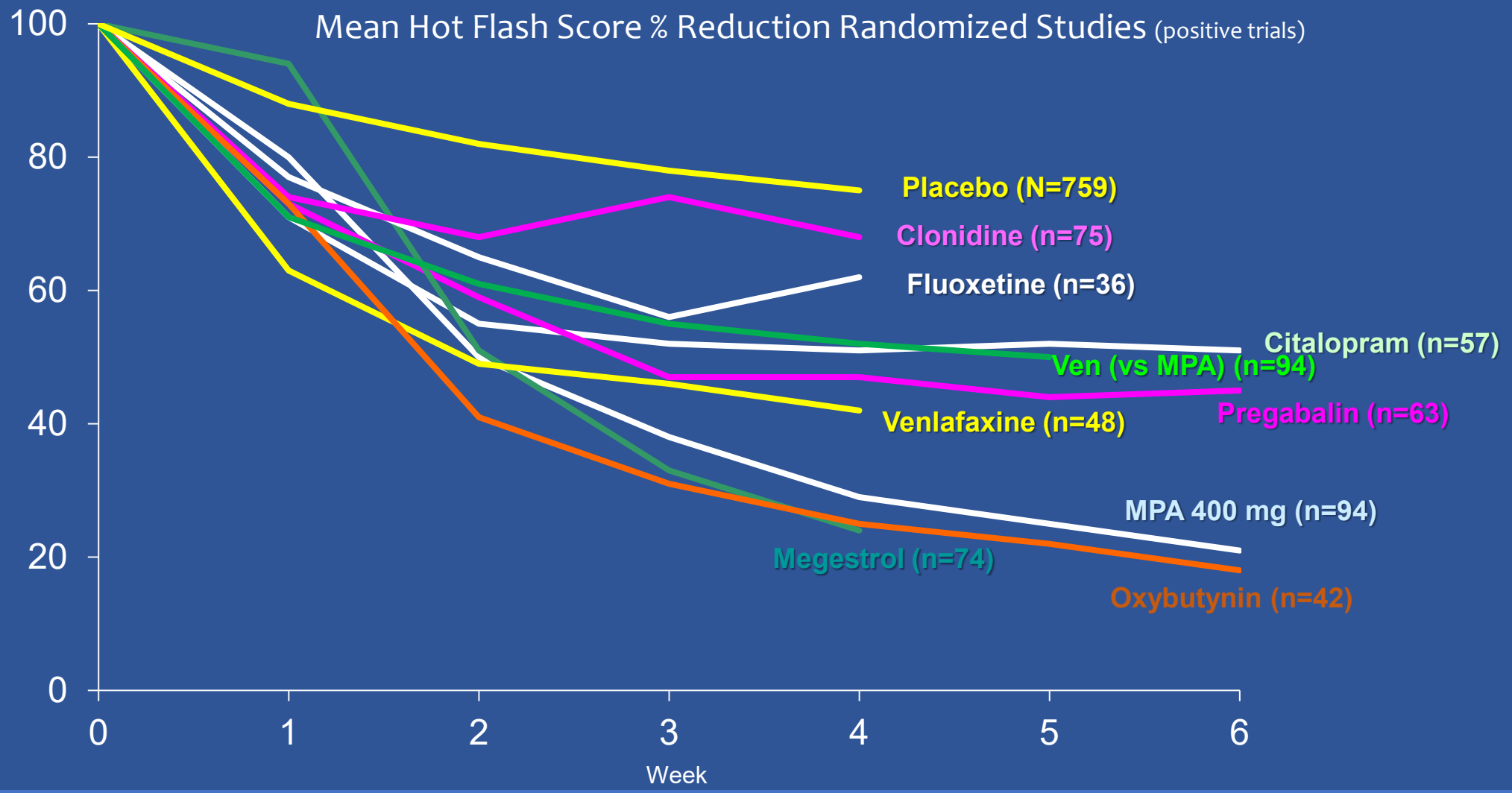
Nelson HD et al JAMA 2006;295(17): 2057-2071
NAMS position statement. Menopause. 2015;22(11):1155-1172.

OXYBUTYNIN

- Antimuscarinic, anticholinergic therapy
- Used for overactive bladder and urinary urge incontinence
- Doses from 2.5 to 5 mg BID up to 15 mg extended release daily
  - Significantly improved moderate to severe vasomotor symptoms
- Adverse events: (dose- dependent) dry mouth, urinary retention
  - *Long term use of anticholinergics may be associated with cognitive decline, particularly in older people*

Kim WO et al. ActaDermaVenereo.2010
Simon JA et al. Menopause 2016
Leon-Ferre RA et al. JNCI Cancer Spectr. 2020
Duong V et al. Int urgogynecol 2021

How does this compare with other HF trials?



CASE 1: WRAP UP

- Rose presents with hot flashes & night sweats
- PMH: Unprovoked DVT anticoagulated for 3 months
- FH: DVT in 2 uncles, 1 cousin
- Her vitals, labs and exam are unremarkable.

<u>Prescribe paroxetine 7.5 mg nightly</u>

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CASE 2: MONICA 44 YO ENGINEER

- She presents with significant vasomotor symptoms.
- History of ER/PR positive breast cancer 1 year ago s/p lumpectomy and radiation, now on tamoxifen.

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POLL OPEN

CASE 2

WHAT CAN YOU OFFER HER?

1 Transdermal estradiol + oral micronized progesterone

0%

2 Paroxetine mesylate 7.5 mg daily

0%

3 Venlafaxine 37.5 mg x 1 week, then increase to 75 mg daily

0%

CASE 2

What can you offer her?

- Transdermal estradiol + oral micronized progesterone
- Paroxetine mesylate 7.5 mg daily
- **Venlafaxine 37.5 mg x 1 week, then increase to 75 mg daily**

TAMOXIFEN

- Hot flashes 1 of the most common side effects
  - 80% of women, 30% rate as severe
  - Premenopausal women more likely
- Strong CYP2D6 inhibitors have the potential to adversely affect drug efficacy
  - paroxetine, fluoxetine
- Consider meds with less CYP2D6 4 treatment
  - Venlafaxine, citalopram

Day r. Ann N Y Acad Sci.2001;949:143
Jin Y et al. J Clin Oncol.2008;26(36):5849.
Crandall C. Menopause.2004;11(5):519.

Join: **vevox.app** ID: **XXX-XXX-XXX**

POLL OPEN

CASE 2: PART 2

SHE TELLS YOU SHE DOESN'T WANT TO START AN ANTIDEPRESSANT OR MEDICATION. WHAT DO YOU OFFER HER NOW?

Vote for up to 2 choices

1 Clinical Hypnosis

0%

2 Cognitive behavioral therapy

0%

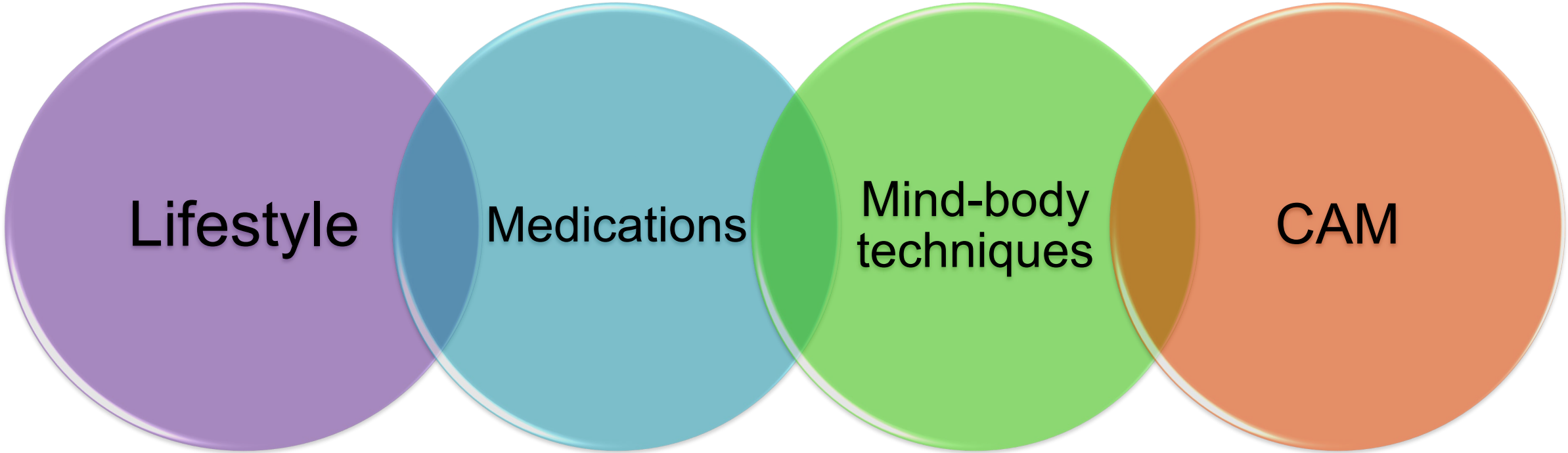
(% = Percentage of Voters)

CASE 2: PART 2

She tells you she doesn’t want to start an antidepressant or medication. What do you offer her now?

- **Clinical Hypnosis**
- **Cognitive behavioral therapy**

MENU OF OPTIONS



MENU OF OPTIONS

- Cognitive behavioral therapy*
  - Self-guided and group formats
- Clinical hypnosis*
- Mindfulness-based stress reduction
  - Acupuncture, yoga, mindfulness meditation
- Pace respiration and relaxation

NAMS 2015 position statement. Menopause.2015;126:859-876.

COGNITIVE BEHAVIORAL THERAPY

- **Includes**:
  - Education on paced breathing
  - Relaxation techniques
  - Psycho-eduction (VMS physiology, stress as a trigger and sleep hygiene)
- Critical to success = expert guidance
  - Regular meetings with clinical psychologist
  - Homework
  - Daily practice on relaxation techniques over weeks

Mann E et al. BMC Cancer.2011;11:44.
Ayers B et al. Menopause.2012;19(7):749-759

CLINICAL HYPNOSIS

- Mind-body treatment that incorporates a relaxed state and mental imagery
- 187 women: weekly therapist directed hypnosis session and at-home self-hypnosis practice over 5 weeks
  - Hypnosis reduced VMS by 74.2% vs. 17.1%
  - Similar findings for physiologically monitored VMS
- Need expertise in VMS hypnosis

Elkins GR et al. Menopause.2013;20(3):291-298.

ACUPUNCTURE

- Ancient practice of traditional Chinese medicine → thin needles inserted into the skin at key points then activated manually or through electrical stimulation (electroacupuncture) to create an energy flow (Qi)
- Several systematic reviewed and meta-analyses evaluated acupuncture vs sham acupuncture, as well as RCTs:
  - Reduced menopause related total scores
  - Improvement in quality-of-life measures
  - Little to no clinical benefit for VMS over sham interventions (symptomatic midlife women and breast cancer survivors)
- 2021 model-based meta-analysis (17 studies)
  - 8 wks electroacupuncture or combo led to significant reduction in VMS/day vs sham

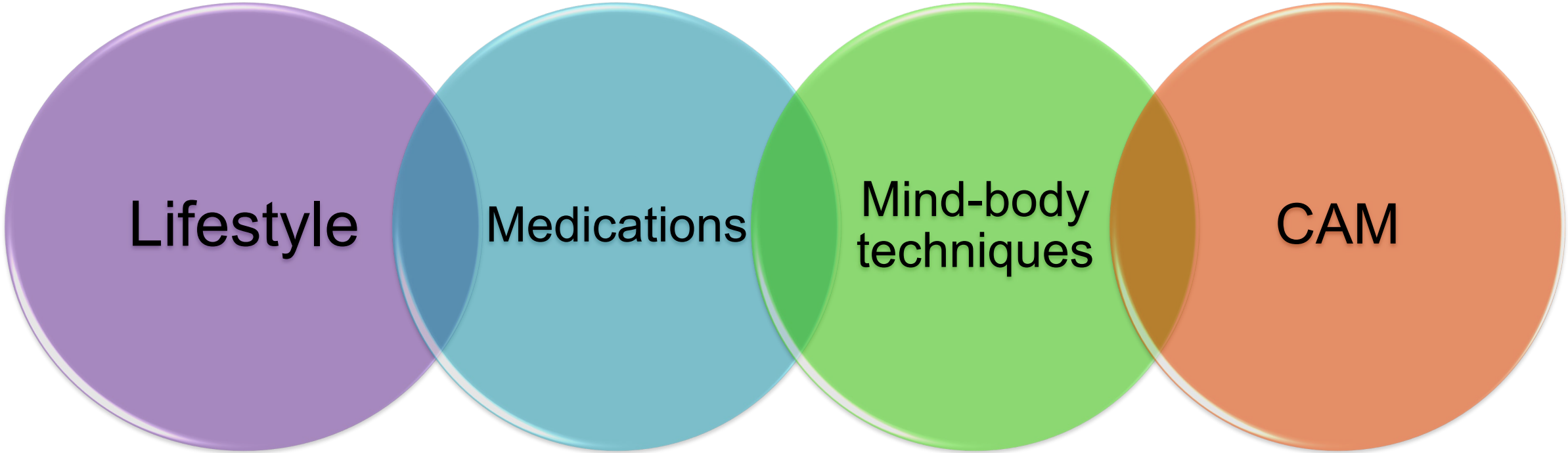
Chien TJ, et al. *PLoSOne*2017; Chien TJ, et al. *Climacteric*2020;
Li T, et al. *Menopause*2021)
Liu Z, et al. *AmJObstetGynecol*2018

CASE 2: PART 3

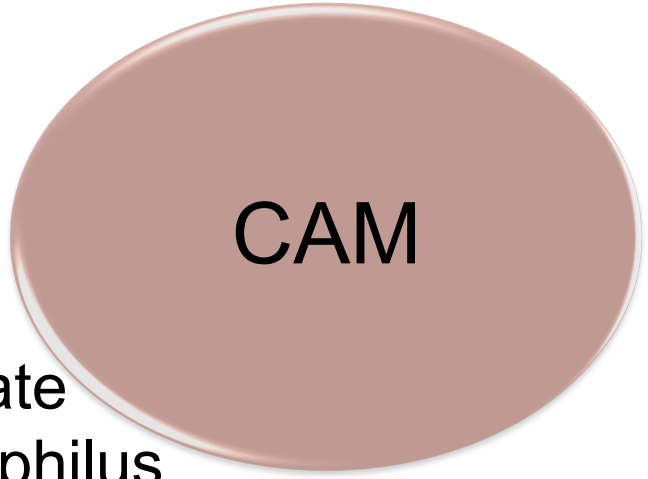
She tells you her friend just started black cohosh and she's wondering if that is something she could consider.

What do you tell her?

MENU OF OPTIONS



MENU OF OPTIONS



- Supplements and herbs
  - black cohosh
  - magnesium oxide
  - red clover
  - soy products
    - soy metabolite equol
  - vitamin E
  - pollen extract
  - Chasteberry
  - Milk thistle
  - Cammabinoids
- Rhubarb
- Wild yam
- Ammonium succinate
- Lactobacillus acidophilus
- Dong quai
- Evening primrose oil
- Maca
- Ginseng
- Eurycoma longifolia
- Omega 3 fatty acids
- Vitamin E

RCTs have not shown them to be more effective than placebo

NAMS 2015 position statement. Menopause.2015;126:859-876.
Stuenkel CA et al. J Clin Endocrinol Metab.2015;100(11)3975-4011.
Newton KM et al. Ann Intern Med.2006:145(12):869-979.

CASE 2 WRAP UP

- 48 yo female with ER/PR positive breast cancer 1 year ago s/p lumpectomy and radiation, now on tamoxifen.
- She presents with significant vasomotor symptoms.

<u>Venlafaxine 37.5 mg x 1 week, then increase to 75 mg daily</u>

MENU OF OPTIONS

- Future options
  - Depomedroxyprogesterone acetate
  - Suvorexant
  - Stellate ganglion block
  - Oral neurokinin receptor antagonist

DEPOMEDROXYPROGESTERONE ACETATE

- Progestational agents decrease hot flashes
  - IM MPA better than oral megestrol
- 400 mg IM dose of depomedroxyprogesterone acetate (MPA) x 1
- 218 patients depot MPA vs. venlafaxine
  - 79% vs. 55% ($p<0.0001$)
  - Less toxicity reported in MPA arm
- Case control cohort study at tertiary academic center looking at women with breast cancer vs. without (Median follow up 68.4 mo in cases)
  - No significant impact on local regional recurrence rate or progression free survival over that time. Women reported good improvement in VMS
- Side effects: Cognitive, bleeding, GI side effects
- Long term safety?

Loprinzi et al. J Clin Oncol 2006 24:1409-1414
Loprinzi CL, et al: N Engl J Med 331: : 347,1994 -352
Loprinzi CL, N Engl J Med 331: 347,1994 -352
Bertelli G, Ann Oncol 13: : 883,2002 -888

SUVOREXANT

- Dual orexin-receptor antagonist that blocks the hypothalamic neuropeptide orexin-A → treats insomnia
  - May be involved in hot flash occurrence
  - Postmenopausal women have plasma levels 3X higher than premenopausal women → lead to sleep disruption & impaired thermoregulation

- Small randomized study of menopausal women showed reductions in nighttime vasomotor symptoms with suvorexant vs placebo
  - Did not improve daytime symptoms

Rahman SA, et al. *SleepJ*2022
Herring WJ, et al. *BiolPsychiatry*2016; Herring WJ, et al. *SleepMed*2019;
Herring WJ, et al. *JClinSleepMed*2016

STELLATE GANGLION BLOCK

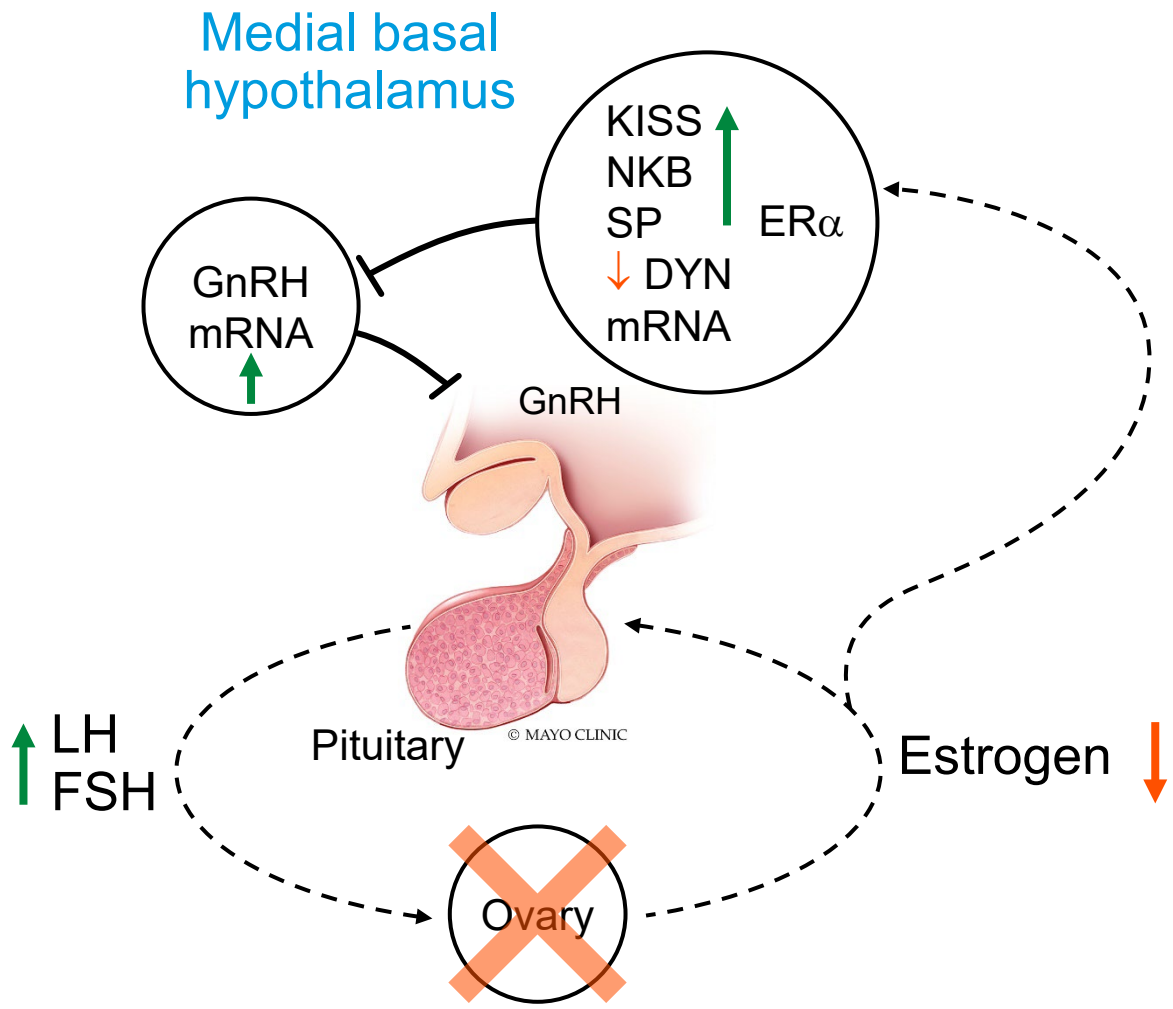
- Administered by a pain specialist

- Blocks the cervical sympathetic chain (used to treat certain pain syndromes)
  - ??Interruption to sympathetic nervous system affects norepinephrine levels within the thermoregulatory area of the brain

- Reduces VMS frequency when compared to sham

Lipov EG et al. Med Hypotheses.2009;72(6):657-661
Walega DR et al. Menopause.2014;21(8):807-814.

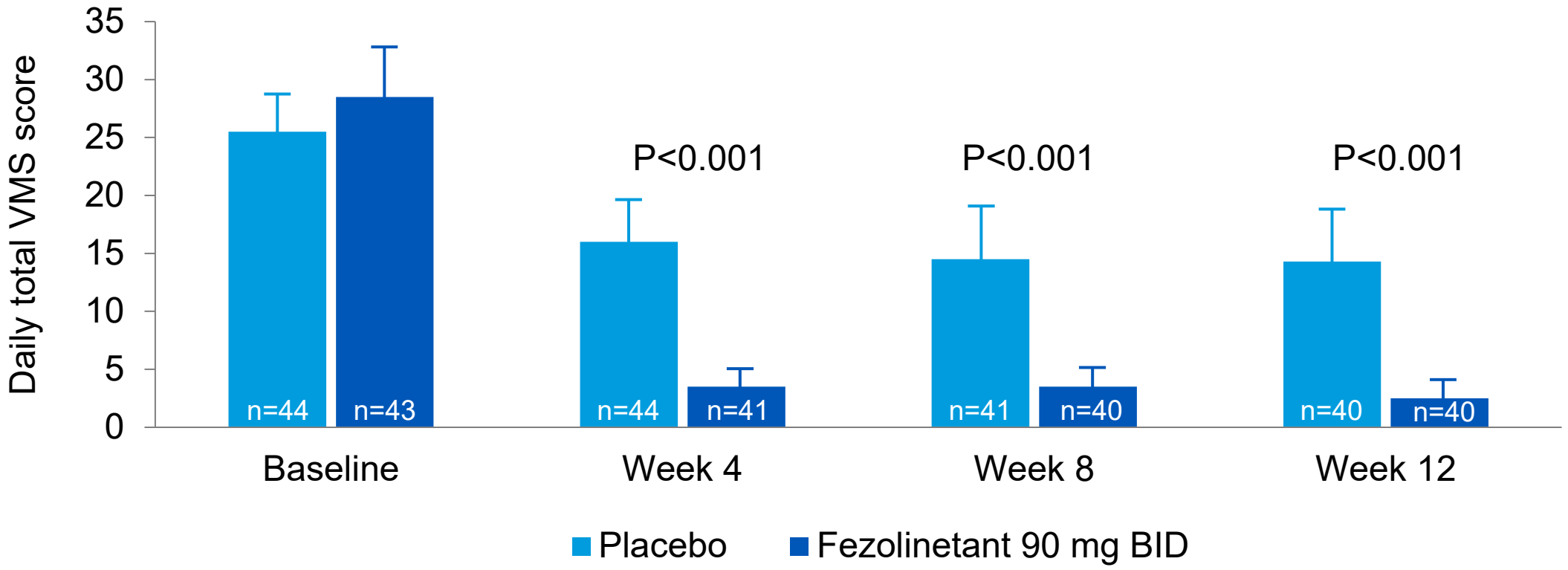
PROPOSED KNDy NEURON LINK TO HOT FLASHES



- Loss of feedback regulation of hypothalamic gonadotropin release hormone (GnRH) during menopause
- NKB neurons key link between endocrine changes & vasomotor symptoms
- Fezolinetant (NKB 3 antagonist)
- Elinzanetant (NKB 3 &1 antagonist)

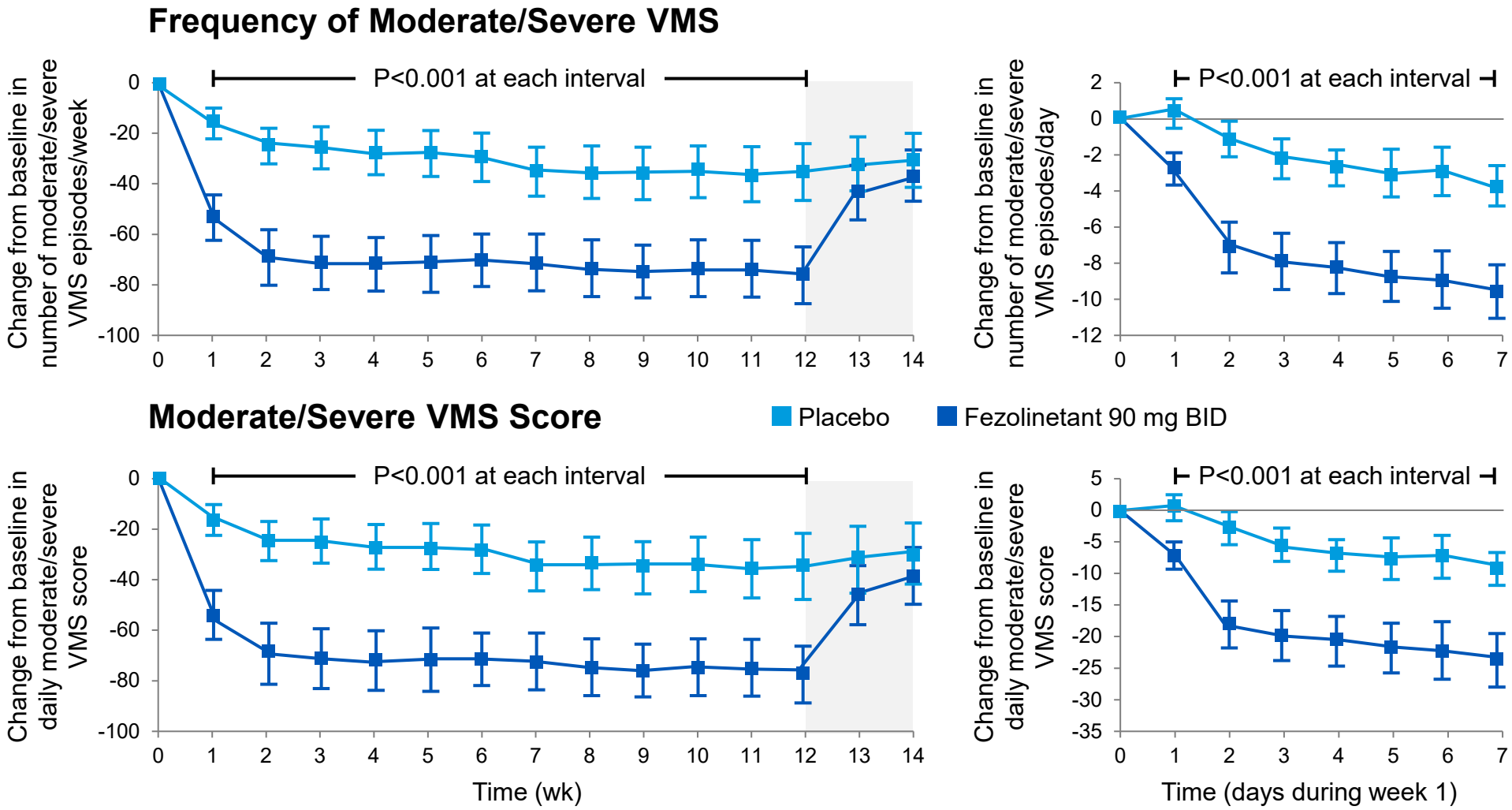
Goodman RL, et al. *J Neuroendocrinol*2022

PHASE 2a TRIAL OF NK3 RECEPTOR ANTAGONIST FEZOLINETANT



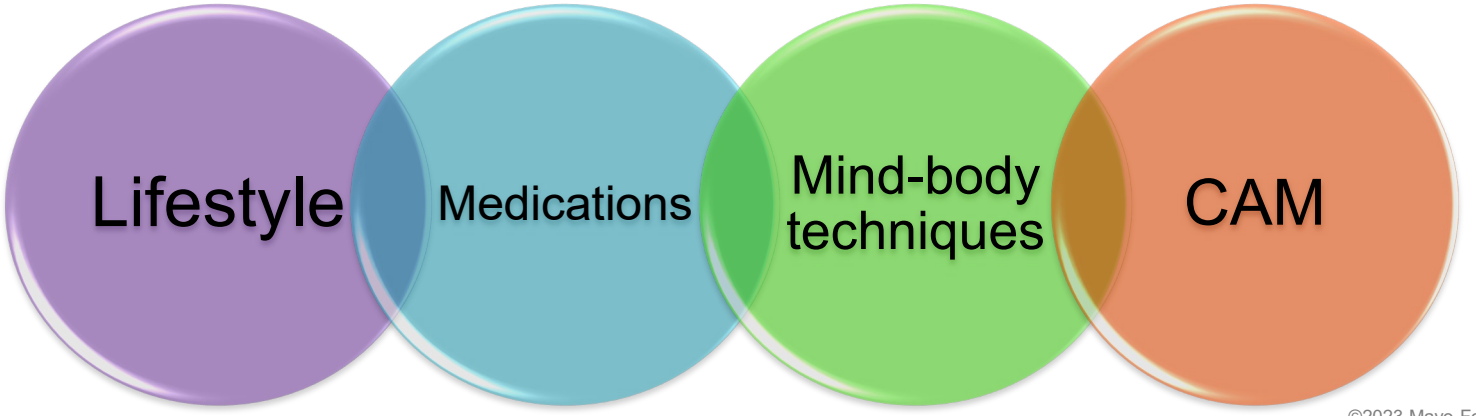
Fraser GL, et al. *Menopause*2020; Trower M, et al. *Menopause*2020

PHASE 2a TRIAL OF FEZOLINETANT

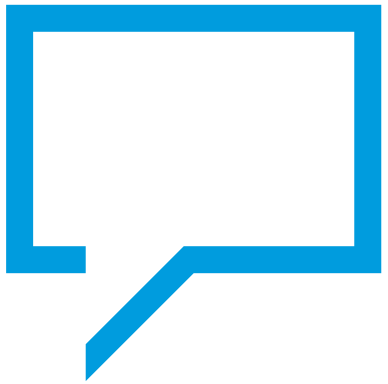


IN SUMMARY

- A menu of non-hormonal options for menopause symptoms is available
  - including emerging therapies
- The North American Menopause Society has a position statement that can help guide your treatment
  - Look out for updated position statement in summer!



QUESTIONS & DISCUSSION



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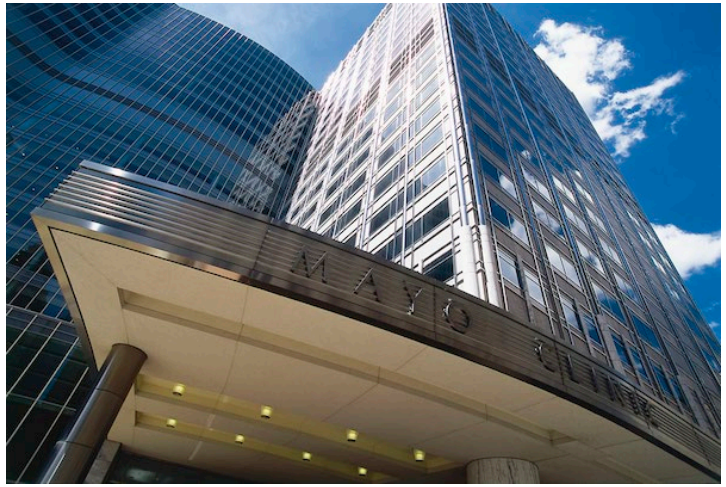
THANK YOU FOR JOINING US IN THIS COURSE



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