Vasomotor Symptoms: What's New, What Works? Pharmacologic Treatment Options and Menopause Management Strategies

ACP ANNUAL MEETING

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Disclosures

Conflicts of Interest, Off-Label Use, Trade Names, Definitions, and Abbreviations

Disclosures:
- Royalties from UpToDate
- NIH research funding
- Bayer, AG research funding

Conflicts of Interest: None

Off-label Drug Use: SSRI/SNRIs (Selective Serotonin Reuptake Inhibitors / Selective Norepinephrine Reuptake Inhibitors), Gaba-ergics, clonidine, oxybutynin

Trade Names: Every attempt was made to present in a nonbiased fashion

Definitions: EPT = estrogen + progestin, ET = estrogen only

Abbreviations:
- KNDy = Kisspeptin, Neurokin B, Dynorphin
- NKB = Neurokinin B
- NK3R = Neurokinin 3 receptor
- NK1R = Neurokinin 1 receptor

Use of the Term "Women": Individuals who do not consider themselves women experience menopausal VMS; all efforts to use gender neutral language are made

MsFLASH Investigators (2008-2022)

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Objectives

- Review menopause management principles for the office
- Describe efficacy and safety of the newest therapies for menopausal hot flashes, including
  - KNDy therapeutics
  - New estrogen, estetrol (E4)

Women Have Been Misled About Menopause

Hot flashes, sleeplessness, pain during sex: For some of menopause’s worst symptoms, there’s an established treatment.

Why aren’t more women offered it?

Source: Susan Dominus, New York Times February 2023

Following shared decision making in an otherwise healthy 50-59 year old without risk factors for hormonal therapy

Is MHT too risky to prescribe?

A. yes

B. no

Background

- MHT remains the gold standard for treatment of VMS
- Only 25% - 40% of patients seek medical RX for VMS

- 2020 survey of menopause providers (N=115 PCP, 118 GYN) and their patients (n=854) and chart review (N=1816) from 5 European countries and US:

  - up to 30% of patients felt they had contraindications to hormones

- 2021 survey of women ≥12 months amenorrhea age 40-65 *without breast cancer* Europe, US and Japan (N= 3460)

  - 60% reported a potential relative contraindication

- HealthyWomen survey (N= 1818) respondents **who opted not to use MHT (34.5%) or stopped using it (44.3%), felt that it was too risky**

Source: UpToDate, August 2023. Stute P. Maturitas 2022 Jun 23;164:38-45. Nappi RE. Menopause 2021;28:875-82. HealthyWomen survey (unpublished) 2023.

Menopausal Hormone Therapy Contraindications

- Contraindications for oral and transdermal hormone therapy include:
  - Unexplained vaginal bleeding
  - Liver disease
  - Prior estrogen sensitive cancer (including breast cancer)
  - Prior coronary heart disease (CHD), stroke, MI, or VTE
  - Personal history or inherited high risk of thromboembolic disease

The Menopause Society™
Leading the Conversation

It is estimated that **~ 10%** of patients with VMS may have contraindications to MHT. **There is a complete disconnect here.**

Source: The 2022 hormone therapy position statement of The North American Menopause Society. Menopause 2022 Jul 1;29(7):767-794. Nappi RE. Menopause 2021;28:875-82. DePree B. Menopause 2023;30:887-97. https://gis.cdc.gov/Cancer/USCS/#/NationalPrevalence/

Who is to blame for this misinformation?

- Researchers and scientists
- Healthcare providers
- The media
- Online for-profit companies
- Patients

Source: Getty Images

Menopause toolkit, diagnosis and management

- STages of Reproductive Aging Workshop (STRAW): definitions of reproductive stages https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3340903/
- Study of Women's Health Across the Nation (SWAN): natural history race ethnicity cohort https://www.swanstudy.org/
- HT Equivalencies: essential for proper clinical management
  0.625 mg oral CEE = 1 mg oral E2 = 0.05 mg TD E2 = 0.005 mg oral EE
- Women's Health Initiative (WHI): what is truth and what your patients think is truth about HT https://www.whi.org/
- Menopause Symptoms: Finding Lasting Answers for Symptoms and Health (MsFLASH): hormonal vs nonhormonal therapies https://mymenoplan.org/

STages of Reproductive Aging Workshop (STRAW)

Menarche

FMP (0)

Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine										
FSH			Low	Variable*	↑ Variable*	↑ >25 IU/L**	↑ Variable		Stabilizes	
AMH			Low	Low	Low	Low	Low		Very Low	
Inhibin B			Low	Low	Low	Low	Low		Very Low	
Antral Follicle Count			Low	Low	Low	Low	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2-5 ↑ = elevated

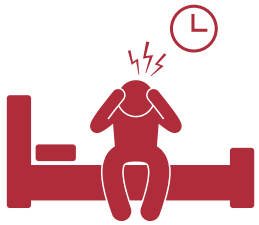
**Approximate expected level based on assays using current international pituitary standard[67-69]

Source: Harlow SD. J Clin Endocrinol Metab. 2012 Apr;97(4):1159.

Menopause Transition
Common Symptoms, Peak 46-56

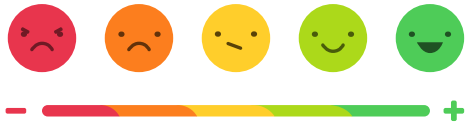
Menstrual irregularity
90%

Hot flashes/night sweats
80%

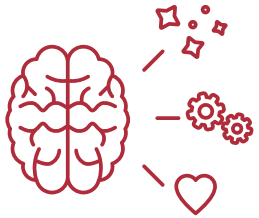


Insomnia
45%

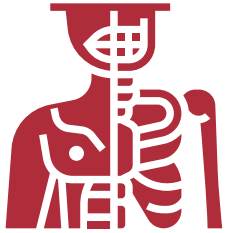
Diminished libido
60%



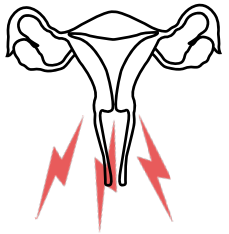
Mood changes/depression
30%



Cognitive changes
45%



Musculoskeletal
50%



Dyspareunia
20%

Predictors of Hot Flash Duration

Shorter	Longer	Median Years
Postmenopause at first symptoms	Pre/perimenopause at first symptoms	3.4 vs 11.8
Japanese/Chinese	AA race	4.8/5.4 vs 10.1
Non-Hispanic	Hispanic	6.5 vs 8.9
Education ≥ college	Education < college	7.7 vs 9.9
Stress never/almost never	Stress at least sometimes	8.9 vs 10.8
No depression	Depression	7.7 vs 11.0
No anxiety	Anxiety (mild-severe)	5.0 vs 7.4

Other factors predictive of longer hot flash duration:

- Financial strain
- Single
- Smoker
- Poor social support
- BMI >30 kg/m2

Source: Avis NE (SWAN). JAMA Intern Med 2015;175(4):531-9.

MENOPAUSAL HORMONE THERAPY

Oral Contraceptives* vs. Postmenopausal Estrogen Dose "Effective Equivalencies"

STANDARD ESTROGEN DOSE EQUIVALENCIES

- Oral conjugated equine estrogen 0.625 mg
- Oral estradiol 1 mg
- Transdermal estradiol 0.050 mg
- Oral ethinyl estradiol* 0.005 mg

Case #1

52 years old

- Worsening hot flashes and night sweats interfering with sleep and work
- Hysterectomy age 49 (still has ovaries)
- BMI 31 kg/m2
- Healthy otherwise with no medical comorbidities or concerning family history
- Asks for the new NKB antagonist (fezolinetant, Veozah™) she saw on TV ad

What are treatment options?

Case #1

A. Oral conjugated equine estrogen 0.625 mg
B. Oral estradiol 1 mg
C. Transdermal estradiol 0.05 mg (gel)
D. Transdermal estradiol 0.45 mg/ levonorgestrel 0.015 mg
E. Oral fezolinetant 45 mg

Case #2

50 years old

- Severe menorrhagia, menses q 28-36 days x 5-7 d
- Worsening hot flashes and night sweats interfering with sleep and work
- BMI 30 kg/m2
- Healthy otherwise with no medical comorbidities or concerning family history

What are treatment options?

Case #2

Case #2

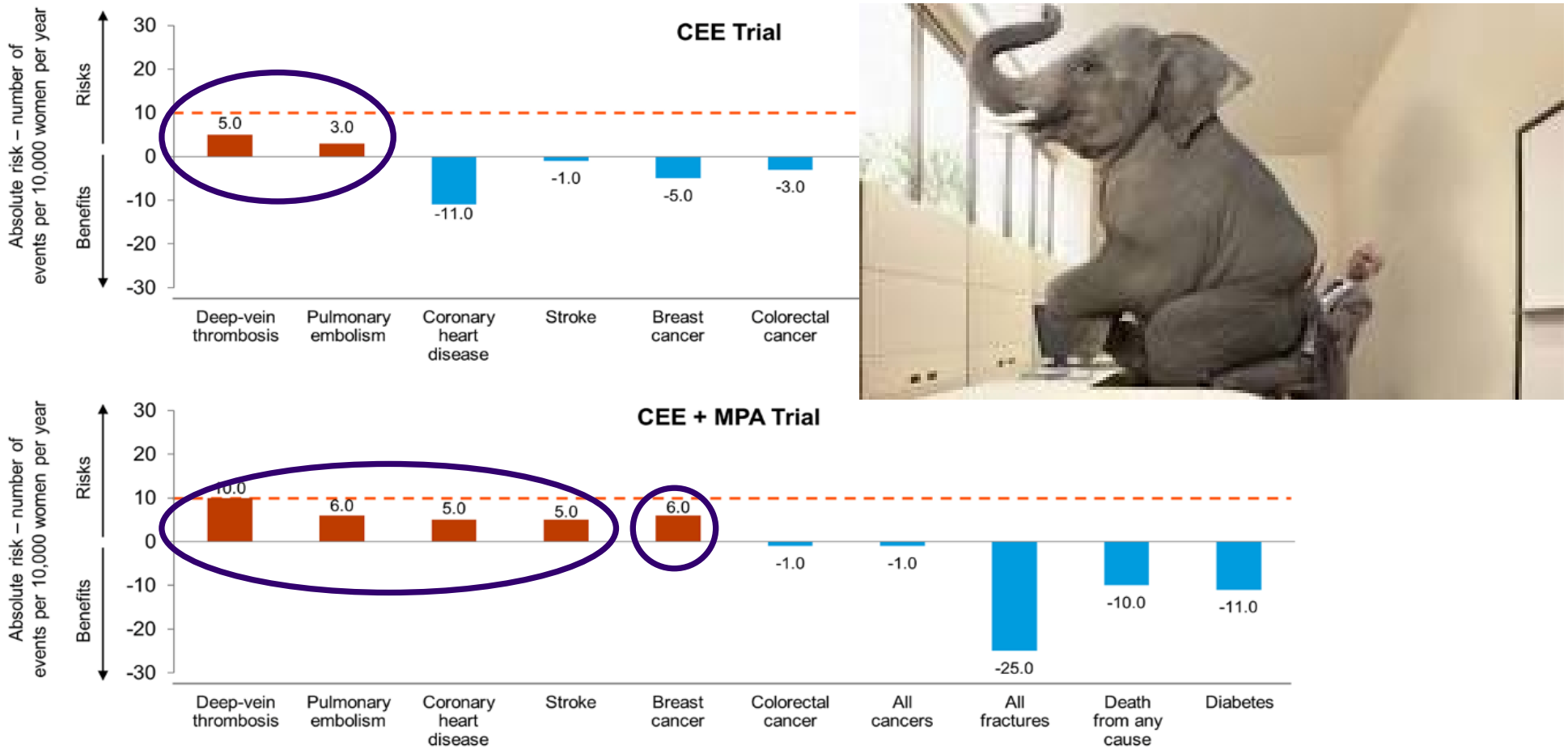
A. Oral conjugated equine estrogen 0.625 mg/ medroxyprogesterone acetate 2.5 mg
B. Oral estradiol 1 mg
C. Transdermal estradiol 0.05 mg (patch) and levonorgestrel IUS 52 mg
D. Transdermal estradiol 0.05 mg/ norethindrone 0.14 mg
E. Bioidentical transdermal estradiol 0.05 mg patch and oral micronized progesterone 100 mg

Effective Hormonal Therapies

- Relatively safe for all healthy women up to age 60 or within 10 years of FMP, especially those without uterus (caveat breast cancer risk)
- HT is best choice for (in absence of contraindications):
  - Moderate to severe hot flashes
  - VMS with bothersome AUB
  - POI +/- VMS

Source: The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause* 2022 Jul 1;29(7):767-794.
Manson J. *JAMA* 2013;310(13):1353–1368.

WHI findings, ages 50 to 59 years, ET vs EPT



Absolute risk difference in number of events (number in the hormone therapy group minus the number in the placebo group) per 10,000 women per year, with <10 per 10,000 per year representing a rare event (dashed red line), Red = increased risk, blue = decreased risk. Adapted from Manson JE, et al. *JAMA* 2013;310:1353-1368.

Source: The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause* 2022 Jul 1;29(7):767-794.

Menopausal Hormone Therapy Risks

- Overall, the increased absolute risks associated with EPT and ET are rare in those without contraindications (< 1/1000 person years). (Level 1)
- ET and EPT increase risk for VTE and gallbladder disease. (Level 1)
- EPT also increases risk for stroke and breast cancer, and if estrogen is not adequately opposed, increases risk of endometrial hyperplasia and endometrial cancer. (Level I)
- Appropriate formulation, dose, and route of administration of progestogen is needed to counter proliferative effects of systemic estrogen on endometrium, e.g. micronized progesterone. (Level I)

Source: The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause* 2022 Jul 1;29(7):767-794.

MHT Efficacy has been known for years

Better messaging to dispel safety and efficacy myths

- Oral HT most effective treatment for VMS vs placebo (Level I)
  - reduces weekly symptom frequency by 75%, (95% CI, 64.3-82.3) and
  - reduces symptom severity by 87% (odds ratio [OR], 0.13; 95% CI, 0.07-0.23)
  - no other pharmacologic or alternative therapy found to provide more relief
- EPT appears slightly more effective than ET alone. (Level I)
- Various formulations, doses, and routes of prescription hormone therapy preparations have comparable high efficacy for relieving VMS. (Level I)

↓ ~ 2.6 HF/d over PLCBO

Source: The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause* 2022 Jul 1;29(7):767-794.
Maclennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev 2004:CD002978

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Menopausal Hormone Therapy Benefits Beyond VMS

- Reduces bone loss and reduces risk of fracture (33% reduction in WHI) (Level 1)
- Reduces new onset diabetes risk (Level 1)
- Reduces all cause mortality (Level 1)
- ET reduces coronary heart disease when started <age 60 and/or within 10 years of menopause onset (Level 1)
- ET reduces breast cancer risk in women aged < 60 years (Level I)
- May improve mood and depression, sexual function, genitourinary health

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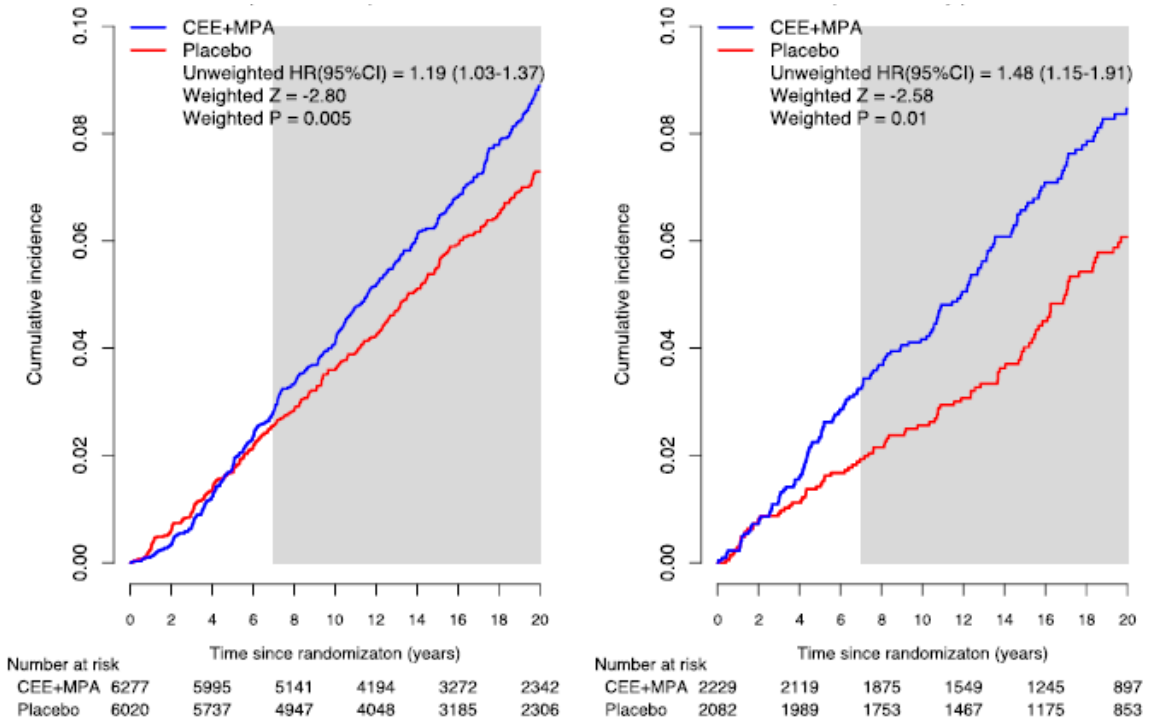
Source: The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause* 2022 Jul 1;29(7):767-794.

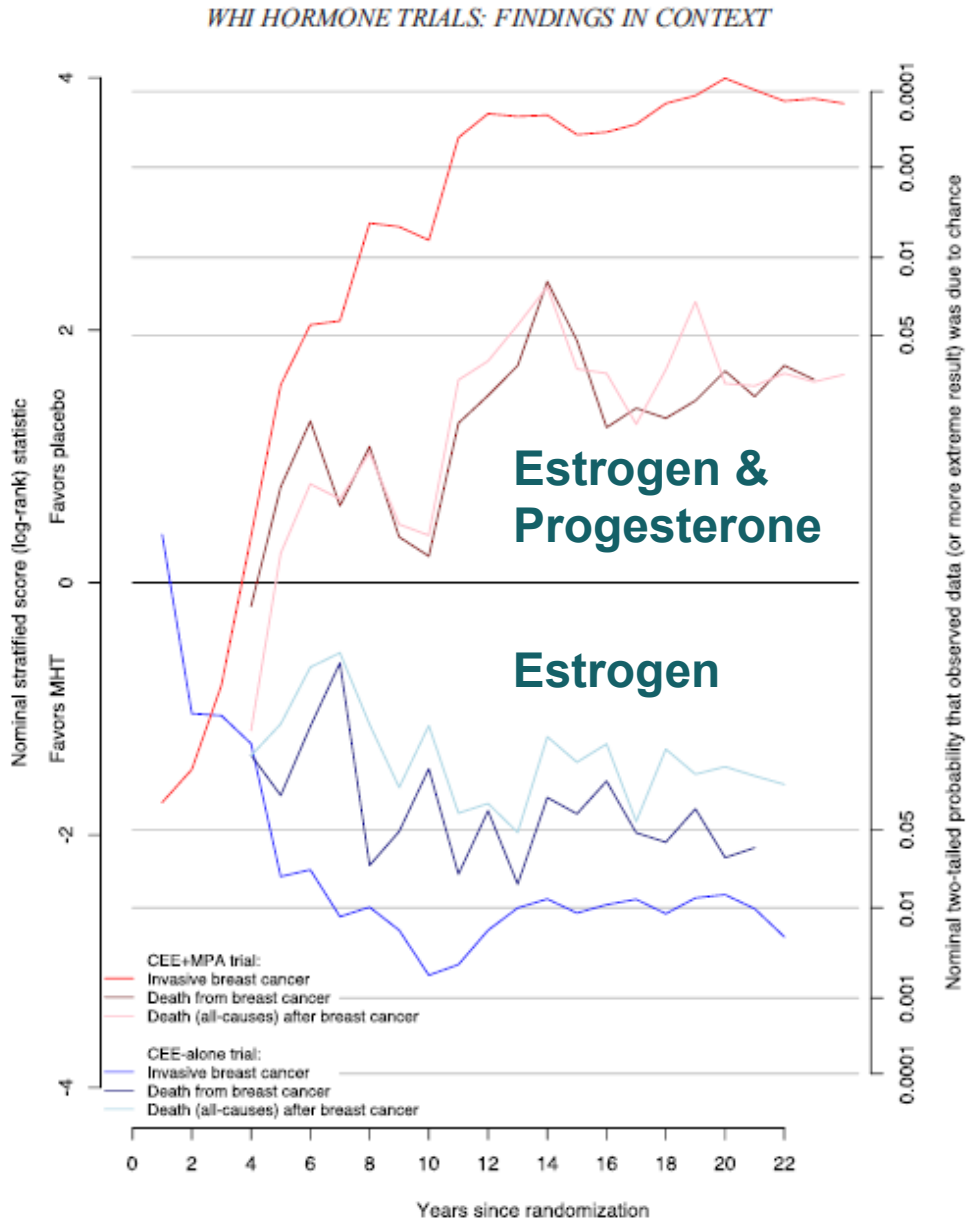
WHI Breast Cancer

CEE-alone (n = 10,739)
CEE plus MPA (n = 16,608)

No prior EPT



Prior EPT



Source: Chlebowski RT. Menopause. 2023 Jan 24

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BREAST CANCER SUMMARY UK COLLABORATIVE

5 years HT use starting at age 50 among average weight individuals in western countries (overweight)*, increases 20-year breast cancer risks among those age 50-69 if using:

- EPT continuous progestogen from 6.3% BL to 8.3%
- EPT cyclical progestogen from 6.3% BL to 7.7%
- ET from 6.3% BL to 6.8%

- Risk varies by weight, background risk: 5.1% lean; overweight 6.3%* and obese 7.2%
- For 10 years of use, 20-year increases in incidence would be about twice as great as for 5 years of use

Source: Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 394 September 28, 2019.

LEVONORGESTREL IUS 52 mg
BREAST CANCER RISK

- Finland post marketing surveillance: IUS placed for menorrhagia

	N	SIR	95% CI
Age 45-49	617	1.23	1.13-1.32
Age 50-54	560	1.30	1.20-1.41
Total	**1,542**	**1.19**	**1.13-1.25**

- Danish Cancer Registry: mean age 40 +/-6 years, **Breast Cancer RR 1.2 (95% CI, 1.1 to 1.3)**

Source: Soini T. Obstet Gynecol 2014:124:202-9
Morch L NEJM 2017; 377:2228-2239.

ESTROGEN DOSE & CVA RISK
ORAL > TRANSDERMAL

- British nested case-control study
- 15,710 stroke cases/59,958 controls, **ages 50-79 yrs**

	Relative Risk (95% CI)
TD low, < 50 mcg vs none:	0.81 (0.62 to 1.05)
TD high, >50 mcg vs none:	1.89 (1.15 to 3.11)
Oral low vs none:	1.25 (1.12 to 1.40)
Oral high vs none:	1.48 (1.16 to 1.90)
TD vs oral:	0.74 (0.58 to 0.95)

Oral users 46% used 0.625 CEE

TD users 68% used 50 mcg E2

Oral low ≤ 0.625 CEE, ≤ 2 mg E2

CVA DX accuracy 89%

Source: Renoux C. BMJ 2010;340:2519.
Lokkegaard E. Stroke 2017;48:2266.
Cho L. Circulation. 2023;147:597–610.

ESTROGEN DOSE & VTE RISK
ORAL > TRANSDERMAL

- British nested case-control study
- 80,396 VTE cases/391,494 controls, **ages 40-79 yrs**

	Relative Risk (95% CI)
TD low, < 50 mcg vs none:	0.94 (0.85, 1.03)
TD high, >50 mcg vs none:	1.05 (0.88, 1.24)
Oral vs none:	1.58 (1.52, 1.64)
Oral vs TD:	1.73 (1.56, 1.85)

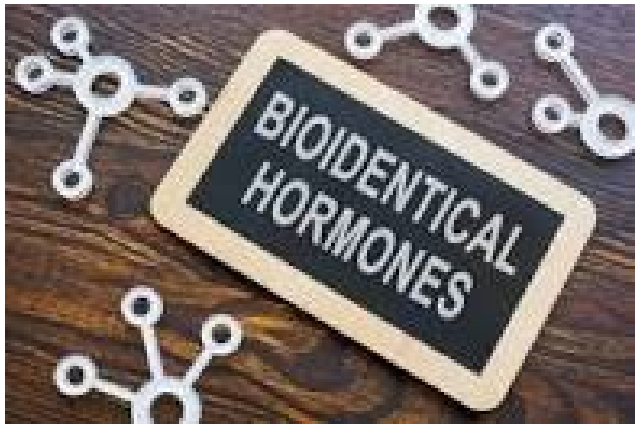
Oral use ~50% CEE, ~ 50% E2

Oral CEE risk > Oral E2 risk

Oral CEE + MPA highest VTE risk

Source: Vinogradova Y. BMJ 2019;364:4810.
Cho L. Circulation. 2023;147:597–610.

BIOIDENTICAL HORMONE THERAPY



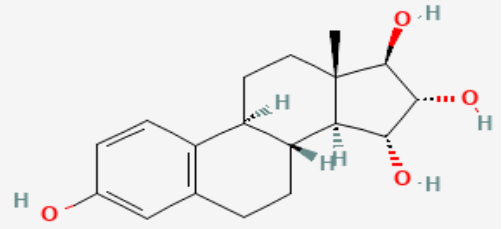
- Patients think bio-identical is better
- There is no data to support this claim
- In fact, there is data to support variable purity, mislabeling with unclear potency and lack of efficacy and safety data

Source: ACOG Committee Opinion # 532, Aug 2012

The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause* 2022 Jul 1;29(7):767-794

Hormonal Therapies

What's New? What's Different?



Estetrol (E4)

- 4th known natural human estrogen
- Only found during pregnancy and is made by fetal liver; function in pregnancy unknown
- Classified as first Natural Estrogen with Selective Action in Tissues (NEST), activating *nuclear* ERα, with antagonistic activities at *membrane* ERα
- May have more favorable properties than estradiol, estrone and estriol with less impact on liver metabolic processes; "no clinically relevant effects on cytochrome P450 liver enzymes"
- May have favorable activity in breast, brain, bone and vaginal tissues
- Does not bind SHBG, has long half-life, 28–32 hours, almost two-fold longer than E2
- E4 metabolites (sufonides and glucuronides) are mainly excreted in urine, not bile

Source: Fruzzetti F. J Clin Med. 2021;10(23):5625. Reame N. Menopause 27(8):p 841-843, August 2020. Gaspard U. Menopause 2020; 27:848–857.

Hormonal Therapies

What's New? What's Different?

Estetrol (E4)

- Estetrol 14.2 mg and drospirenone (Nextstellis®, FDA approval 2021 as **COC**, with coupon $195 for 24)
- **Estetrol 15 or 20 mg, (Donesta®, Phase 3 trials, Mithra Pharmaceuticals anticipate FDA approval 2024)**

Hormonal Therapies

What's New? What's Different?

Bioidentical estrogen and progesterone

- Estradiol 1 mg and progesterone 100 mg (Bijuva®, FDA approved 2018, with coupon $238 for 30)

TSEC

- Bazedoxifene 20 mg and CEE 0.45 mg (Duavee®, FDA approved 2013, average cost $187 for 30)

Source: Pickar, JH. *Menopause* 2018;25(9):1033-1045.

Cost of VMS FDA Approved Estrogen Oral or TD RX

Drug	*Some formulations (mg)*	*Cost ($/mo)*
ESTROGENS ORAL		
CEE (premarin)	0.3, 0.45, 0.625, 0.9, 1.25	177
E2 generic	0.5, 1, 2	1
E2 (Estrace)		163
Est E (Menest)	0.3, 0.625, 1.25, 2.5	75
ESTROGEN TD		
E2 (Alora)	0.025, 0.05, 0.075, 0.1 mg/d patches	113
E2 (Climara)	.025, 0.0375, 0.05, 0.06, 0.075, 0.1/d patches	138
E2 (Vivelle dot)	0.025, 0.0375, 0.05, 0.075, 0.1 /d patches	121
E2 (Estrogel)	0.75 mg/actuation (30 doses/unit)	127
E2 (Divigel)	0.25, 0.5, 0.75, 1, 1.25 mg/packets	87
E2 (Elestrin)	0.52 mg/actuation (100 doses/unit)	36
E2 (Evamist)	1.53 mg/spray (56 sprays/unit)	124
E2 (Femring)	0.05, 0.1 mg/d vaginal rings	532

Source: *JAMA* June 15, 2021 Volume 325, Number 23

Cost of VMS FDA Approved Progestogen RX

Drug	*Some formulations (mg)*	*Cost ($/mo)*
PROGESTIN ORAL		
LNG IUS*	52	12
MP generic	100, 200	26
MP (Prometrium)		317
MPA generic	2.5, 5, 10	3
MPA (Provera)		45
NETA (Aygestin)*	2.5	15
NET (mini pill)*	0.35 mg	17

These products are not FDA approved for contraception, exception LNG IUS and NET 0.35 mg bid

* Off label use for MHT, probably adequate for contraception, indication AUB

Source: *JAMA* June 15, 2021 Volume 325, Number 23

VMS and Choice of FDA approved Estrogen plus Progesterone Oral or TD Cost

Drug	*Some formulations (mg)*	*Cost ($/mo)*
ESTROGEN AND PROGESTERONE ORAL		
CEE/MPA (Prempro)	0.3/1.5, 0.45/1.5, 0.625/2.5, 0.625/5	203
E2/DRSP	0.5/0.25, 1/0.5	186
E2/ NET	0.5/0.1, 1/0.5	256
E2/MP	1/100	215
EE/NET	0.0025/0.5, 0.005/1*	157
ESTROGEN AND PROGESTERONE TD		
E2/LNG (Climara pro)	0.045/0.015 mg/d patches	222
E2/NET (Combi-patch)	0.05/0.14, 0.05/0.25 mg/d patches	207
TSEC		
BZD/CEE (Duavee)	20/0.45	187

**NET 1 mg is a dose approved for contraception in other products*

Source: *JAMA* June 15, 2021 Volume 325, Number 23

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Case #3

51 years old, no menses for 1 year

- History of atypical ductal hyperplasia
- Moderate hot flashes and night sweats
- Tried “non-hormonal therapy, no benefit”

What are treatment options?

Case #3

A. Transdermal estradiol 0.05 mg patch and LNG IUS 52 mg
B. Oral fezolinetant 45 mg
C. Combined transdermal estradiol 0.045 mg/ norethindrone 1 mg
D. Oral conjugated equine estrogen 0.45 mg/ bazedoxifene 20 mg
E. Oral gabapentin 300 mg nightly and venlafaxine 150 mg daily

Effective Non-hormonal Therapies

Gabapentin

Neurontin

Pregabalin

Lyrica

Venlafaxine

Effexor

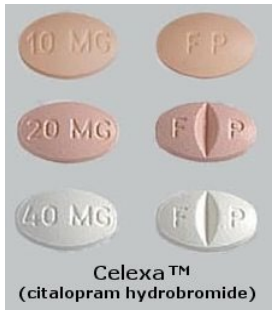
Desvenlafaxine

Pristiq, Khedezla

Paroxetine

Paxil
Brisdelle*

Citalopram



Celexa

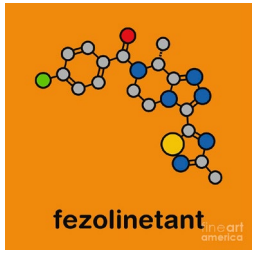
Escitalopram

Lexapro

Oxybutynin

Clonidine

NKB antagonist



Fezolinetant
Veozah*

* FDA approved

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Paroxetine mesylate 7.5 mg vs Placebo
SSRI FDA approved

↓ ~ 1-1.5 HF/d over PLCBO

	Paroxetine	Placebo	
	Median reduction from baseline to 12 weeks of moderate to severe hot flashes per day		Median difference
Study 1 N= 614	5.9	5.0	0.9; P<0.01
Study 2 N=570	5.6	3.9	1.7; P<0.001

Summary: Findings from 2 phase 3 RCTs: Despite a modest effect, more individuals who used paroxetine mesylate than those who used placebo considered the reduction in frequency of their hot flushes to be clinically meaningful by 12 weeks

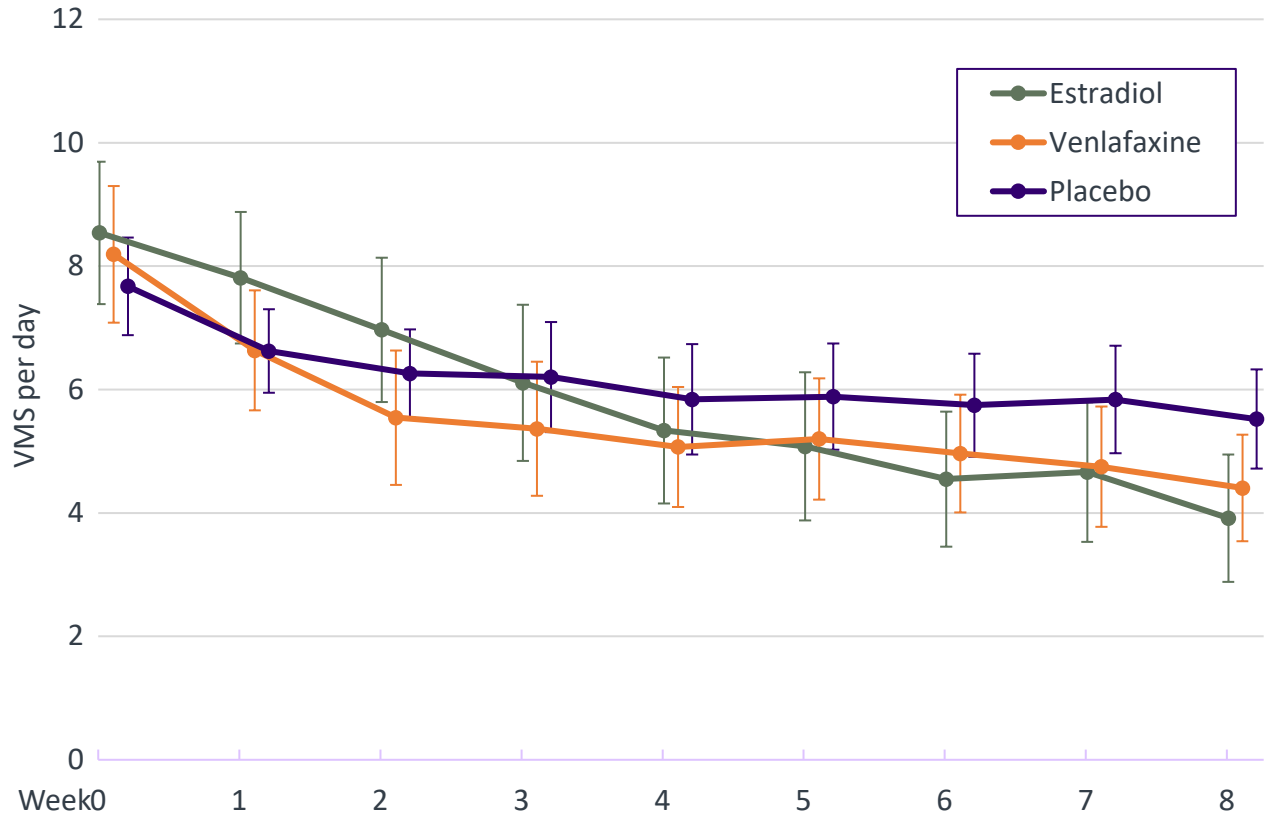
Side effects nausea, dizzy, fatigue higher in intervention group, but all < 4%

Source: Simon JA. Menopause. 2013 Oct;20(10): 1027.

VMS MsFLASH 03, Low Dose Venlafaxine 75 mg vs Estradiol 0.5 mg

How do SSRIs compare with E2?

↓ 1.5-2 HF/d over PLCBO



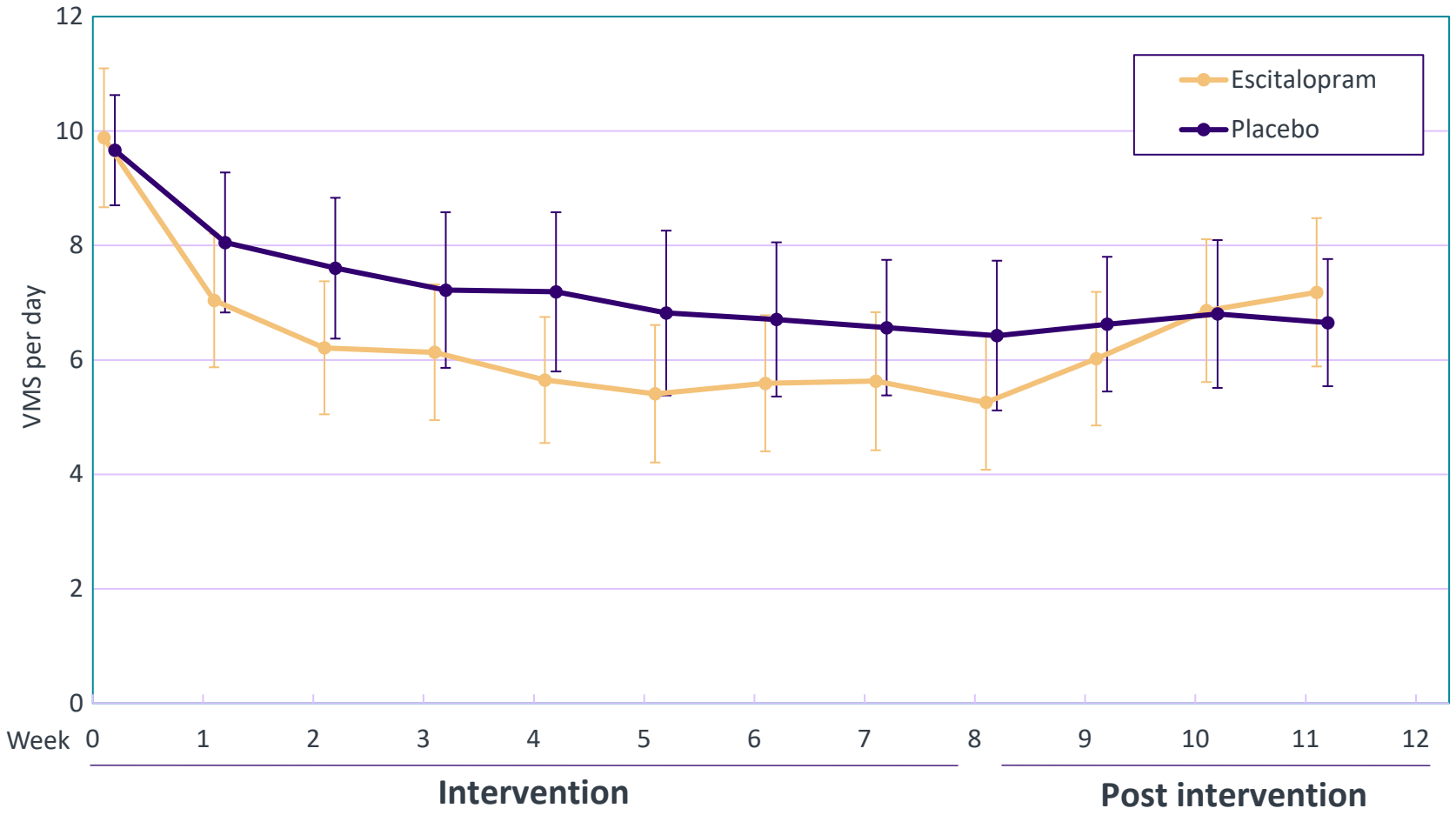
Both venlafaxine and oral low dose estradiol decreased VMS frequency relative to placebo

Source: Joffe H. *JAMA Intern Med* 2014;174(7):1058-66.

VMS MsFLASH 01, Escitalopram 10-20 mg vs Placebo

SSRI with minimal side effects

↓ 1.5 HF/d over PLCBO



Escitalopram rapidly diminished VMS frequency compared to placebo. When the intervention was stopped, the effect rebounded toward baseline.

Source: Freeman EW *JAMA*. 2011 Jan 19;305(3):267-74.

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Gaba-ergics

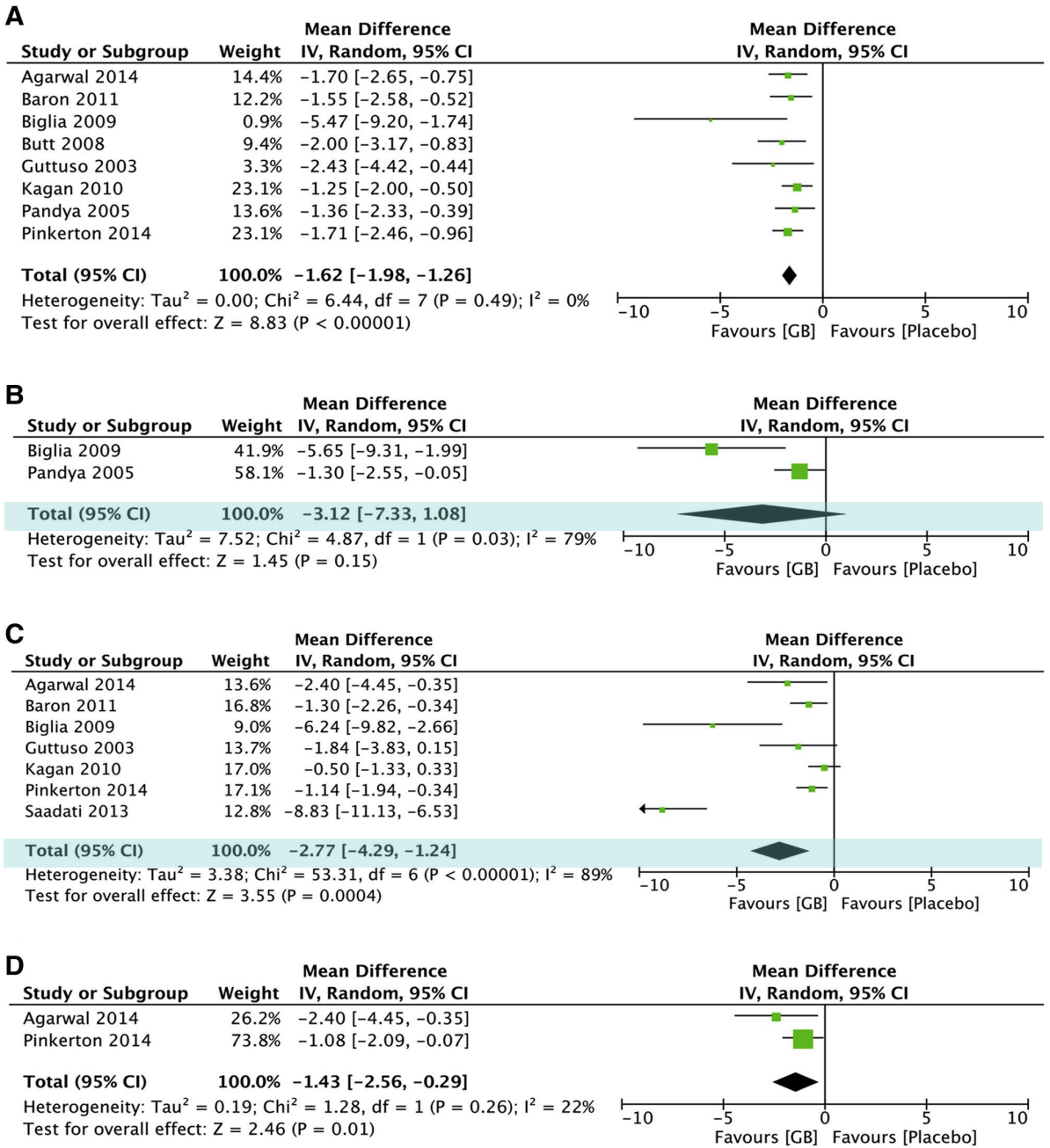
4 weeks

↓ 2.5- 3
HF/d
over PLCBO

8 weeks

12 weeks

24 weeks



Source: Shan D. *AJOG* June 2020.

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Clonidine

Benefit in breast cancer patients but side effects

- RCT 8 wk,194 breast CA patients on tamoxifen, 7.7 HF/d
- Oral clonidine 0.1 mg/d vs plcbo
  - Clonidine decreased 1 HF/day above plcbo (p = 0.006)

Pandya KJ. Ann Intern Med 2000

- RCT 12 wk, 80 breast CA patients, 14 HF/d
- Oral clonidine 0.1 mg/d vs venlafaxine 75mg/d vs plcbo
  - Clonidine and venlafaxine decreased 3.5 and 2.2 HF/d above plcbo (p=0.03 and 0.07, respectively)

Boekhout A, J Clin Oncol 2011

↓ 1-3 HF/d over PLCBO

Rarely used because of side effects: dry mouth, constipation, drowsiness, postural hypotension, poor sleep

Non-Hormonal Therapies

What's New? What's Different?

- Neurokinin B (NKB) antagonists
  - Fezolinetant (FDA approved May 2023)
  - Elinzanetant

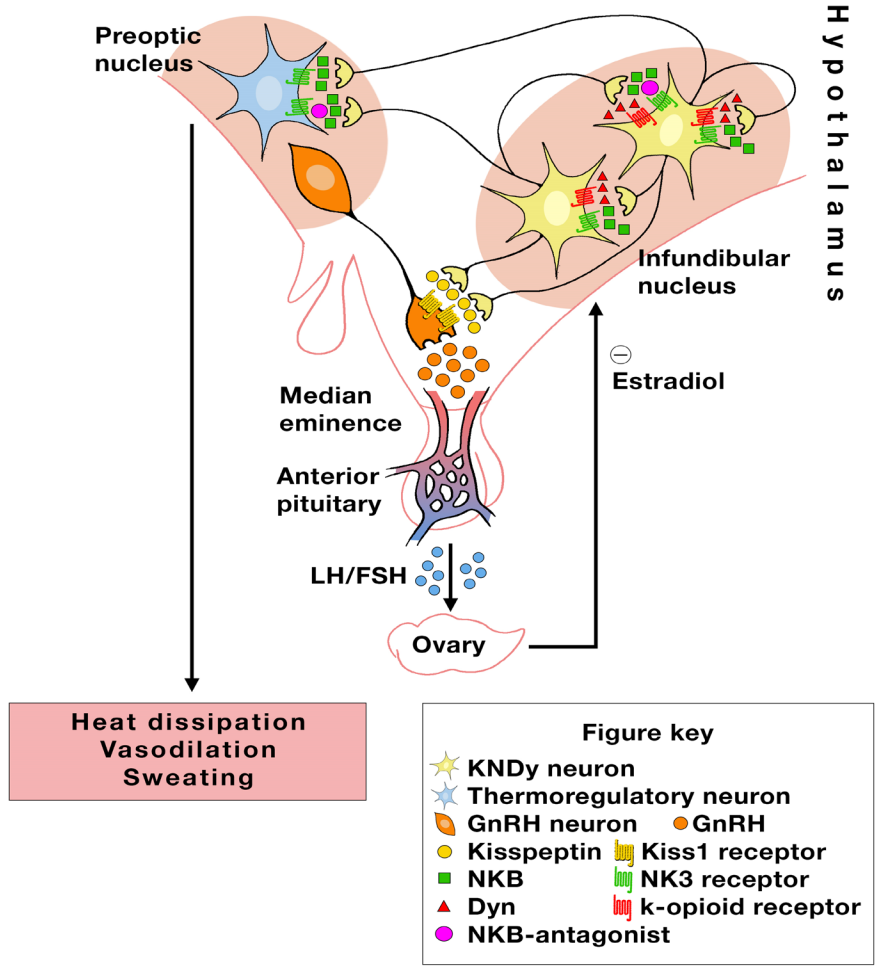
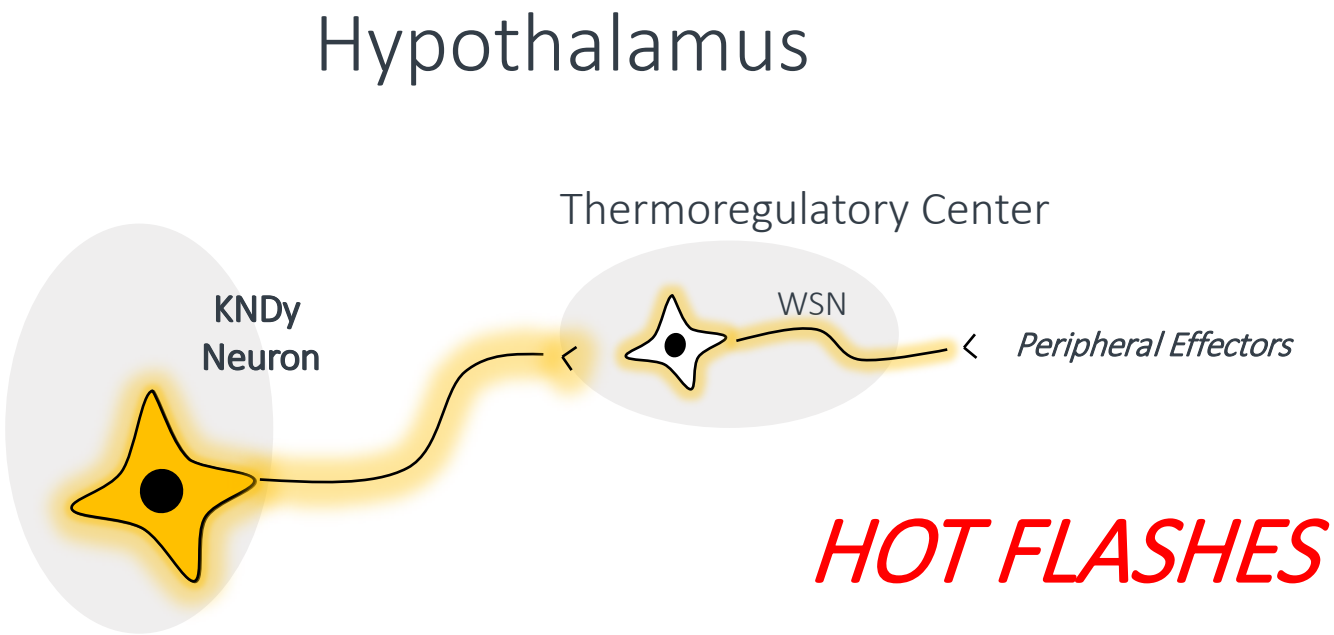


Illustration by Peter J. Christ, BFA, MA

Source: Christ JP, Navarro V, Reed SD. JAMA Insights. August, 2023.

Nonhormonal Therapies
What's New?

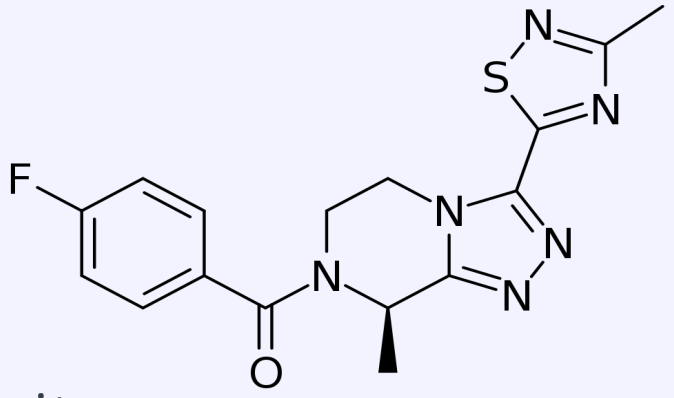
- NKB antagonist



- Hyperactivation of KNDy neurons induces hot flashes by neuronal spill over or excitation of the adjacent thermoregulatory center
- NKB antagonists block this activity

Fezolinetant

Selective NK3R antagonist



- Oral twice daily → daily
- Phase 2 trial VMS STARLIGHT
- Phase 3 trials for menopause SKYLIGHT 1 and 2, 207 sites within the US, Canada and Europe

  N= 1,028
- Also trials in China and Japan

Astellas FDA approved May 12, 2023

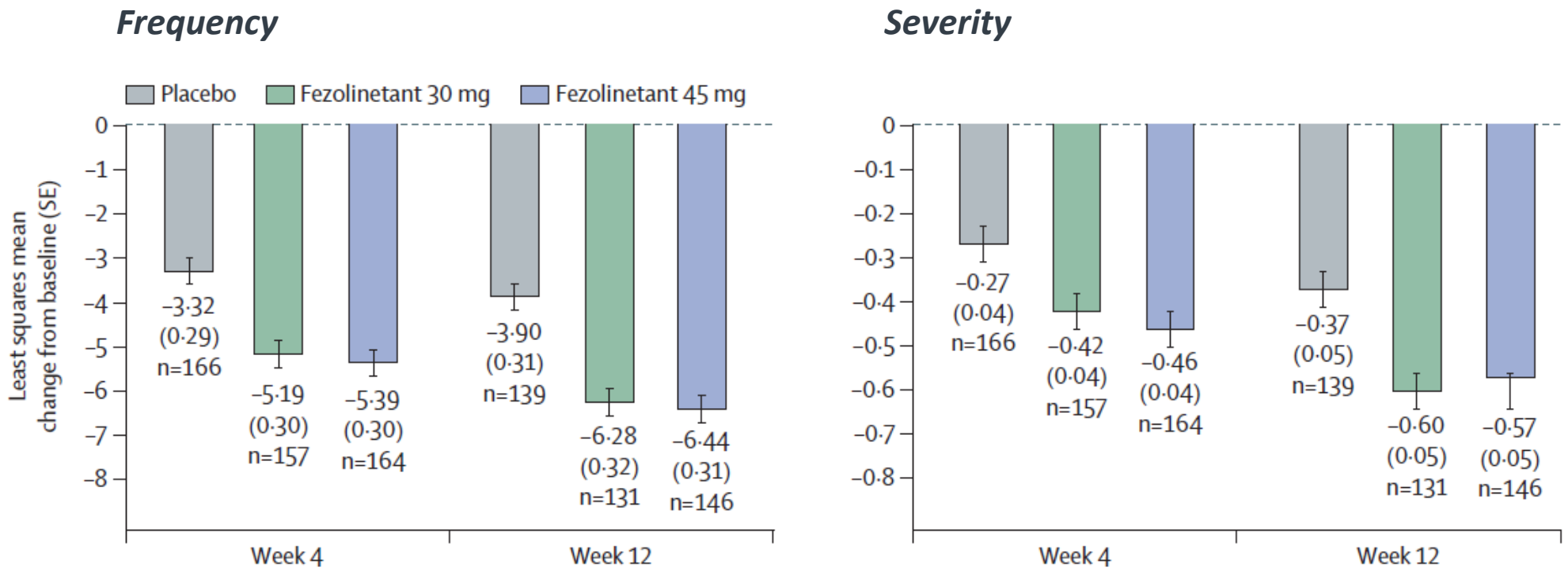
https://bciq.biocentury.com/products/fezolinetant, 14 trials registered in clinicaltrials.gov

Fezolinetant

Frequency & severity of VMS at 12 weeks, and safety to 52 weeks

Phase 3 RCT
SKYLIGHT 1

↓ ~ 2.6 mod-severe HF/d over PLCBO



The incidence of LFT elevations in both SKYLIGHT 1 and 2 was low (placebo n=6[1%]; fezolinetant 30 mg n=8[1.4%]; fezolinetant 45 mg n=12[2%]) and these events were generally asymptomatic, transient, and resolved while on treatment or after treatment discontinuation; **Increased risk neoplasms?**

Source: Lederman S. The Lancet. 2023 Mar 13:S0140-6736(23)00085-5. PMID: 36924778; Johnson KA. J Clin Endocrinol Metab 2023 Feb 3; Neal-Perry G. Obstet Gynecol 2023; 141(4): 737-47. Douxfils J. Lancet Oct 18, 2023

Elinzanetant

Dual NK1R, NK3 antagonist (first-in-class)

Phase 3 studies postmenopausal women OASIS

Anticipate **N~1300,** 200 sites in over 20 countries

Began August 2021, anticipate completion November 2023 and Bayer FDA application early 2024

OASIS 1 Double blind RCT, N=370, 26 weeks

OASIS 2 Double blind RCT, N=370, 26 weeks

OASIS 3 Double blind RCT, N= 600, 56 weeks

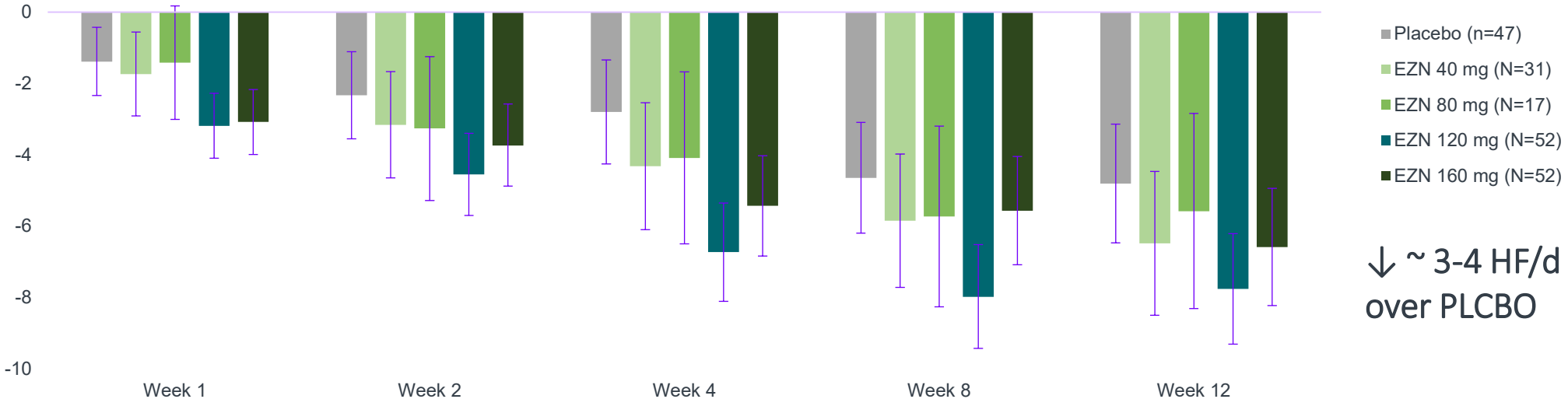
- Dose: **120 mg** vs placebo daily
- Primary outcomes: VMS frequency and severity (12 weeks)
- Secondary outcomes: VMS frequency (1 week) and Sleep, QOL, mood (week 26-56)
- Safety

https://clinicaltrials.gov/NCT05042362
NCT05030584, NCT05099159

Elinzanetant

Phase 2b study postmenopausal women SWITCH-1

- Double blind RCT 12 wk, ≥ 7 mod-severe HF/d, N=199, 25 sites, complete Nov 2019
- Doses: 20 subjects each, placebo vs 40, 80, **120** and 160 mg
- Primary outcomes: VMS frequency and severity (week 4, week 12)
- Secondary outcomes: sleep, mood, QOL



↓ ~ 3-4 HF/d over PLCBO

https://clinicaltrials.gov/NCT03596762; Simon J. S-21. NAMS Annual Meeting, 2020; Panay N. EMAS Annual Meeting, 2021; Figure with permission Halvorson and Bayer. Simon J. Menopause 2023 Mar 1;30(3): 239046.

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Summary NKB Antagonists

	Dec HF freq ~60-80%	Dec HF severity	Improved QOL	Improved Sleep	Sexual function	Side effects
Fezolinetant 45 mg po daily **NK3R antagonist** *FDA approved*	x	x	x	x	No change described AEs	Rare H/A Transient ↑ LFTs (1-2%) **↑neoplasm?**
Elinzanetant 120 mg po daily **Dual NK1R, NK3R antagonist**	x	x	x	x	No change described AEs	Rare somnolence fatigue No △LFT

Cost

VMS and Choice of Pharmaceutical FDA approved RX

Drug	*Some formulations (mg)*	*Cost ($/mo)*
SSRI		
Paroxetine mesylate (generic)	7.5	151
Paroxetine mesylate (Brisdelle)		222
NKB Antagonist		
Fezolinetant	45	550, ~ 67 with insurance

Off label use month supply generic:
gabapentin ($10), venlafaxine ($22), escitalopram ($10)

Source: *JAMA* June 15, 2021 Volume 325, Number 23

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Effective Non-hormonal Therapies

For those with contraindication to HT or those averse to HT:

- Gabaergics, SSRI/SSNRI/ best choice for:
  - **Mild to moderate** hot flashes, or when anticipate shorter treatment period
- NKB antagonist best choice for:
  - **Moderate to severe** hot flashes, needing immediate and long term relief
  - Contraindicated in those with renal or liver disease, need to follow LFTs baseline and q 3 months
  - Expensive
  - Long term data lacking

Summary VMS Pharmaceutical RX

- **For now, HT appears most effective and safe for healthy 50-60 yo**
- Estetrol potential new hormonal RX for menopausal symptoms with possible lower side effect profile
- KNDy neuron manipulation holds great promise for rapid and effective amelioration of hot flashes (60-80%) and improvement in other menopausal symptoms, long term safety data lacking
- SSRIs, SNRIs, GABAergics are best front line non-hormonal options with moderate effect (~50%); clonidine second line due to side effects

- All nonhormonal RX are effective in individuals with and without breast cancer
- Tailor therapy – consider mood, sleep, pain, sexual function, weight gain, gall bladder risk, diabetes, osteoporosis, blood pressure and individual quality of life goals

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Source: Reed SD. Menopause. 2020 Apr;27(4):473-484.

Menopause Toolkit Patient Information, Counseling

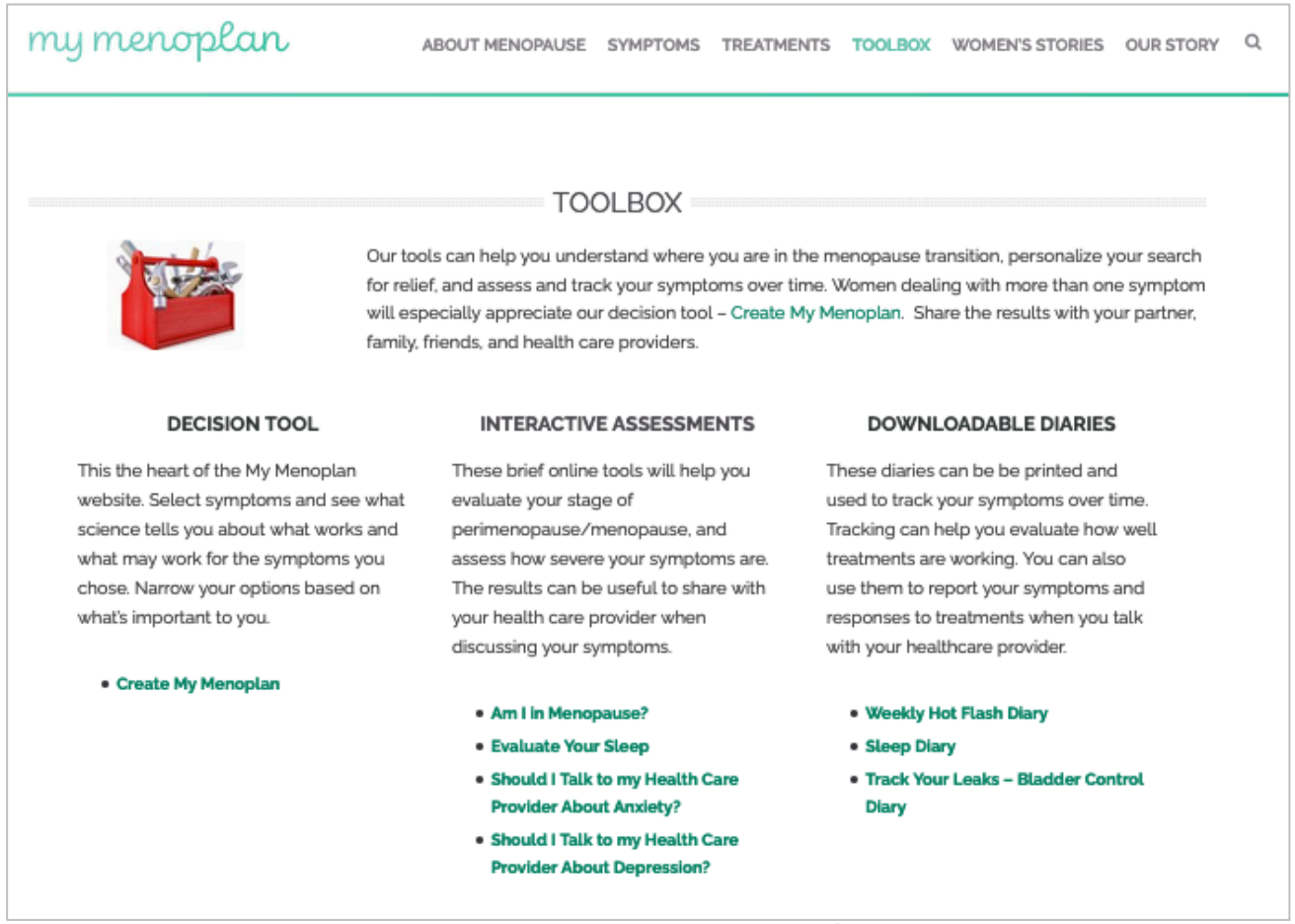
- The Menopause Society
  www.menopause.org
- Women's Health Initiative
  www.whi.org
- MsFLASH
  www.msflash.org, https://mymenoplan.org/
- SWAN (Study of Women's health Across the Nation
  www.swanstudy.org

MsFLASH mymenoplan

Hyperlink to site https://mymenoplan.org/

Tailored Content: Interactive Components

- **“Am I in menopause” tool** based on STRAW criteria, modified to add factors not present in STRAW (IUD, Birth control)
- Validated **screening instruments** (anxiety, depression, sleep)
- Printable **diaries** – VMS, sleep, bladder leaks



Hyperlink to site https://mymenoplan.org/

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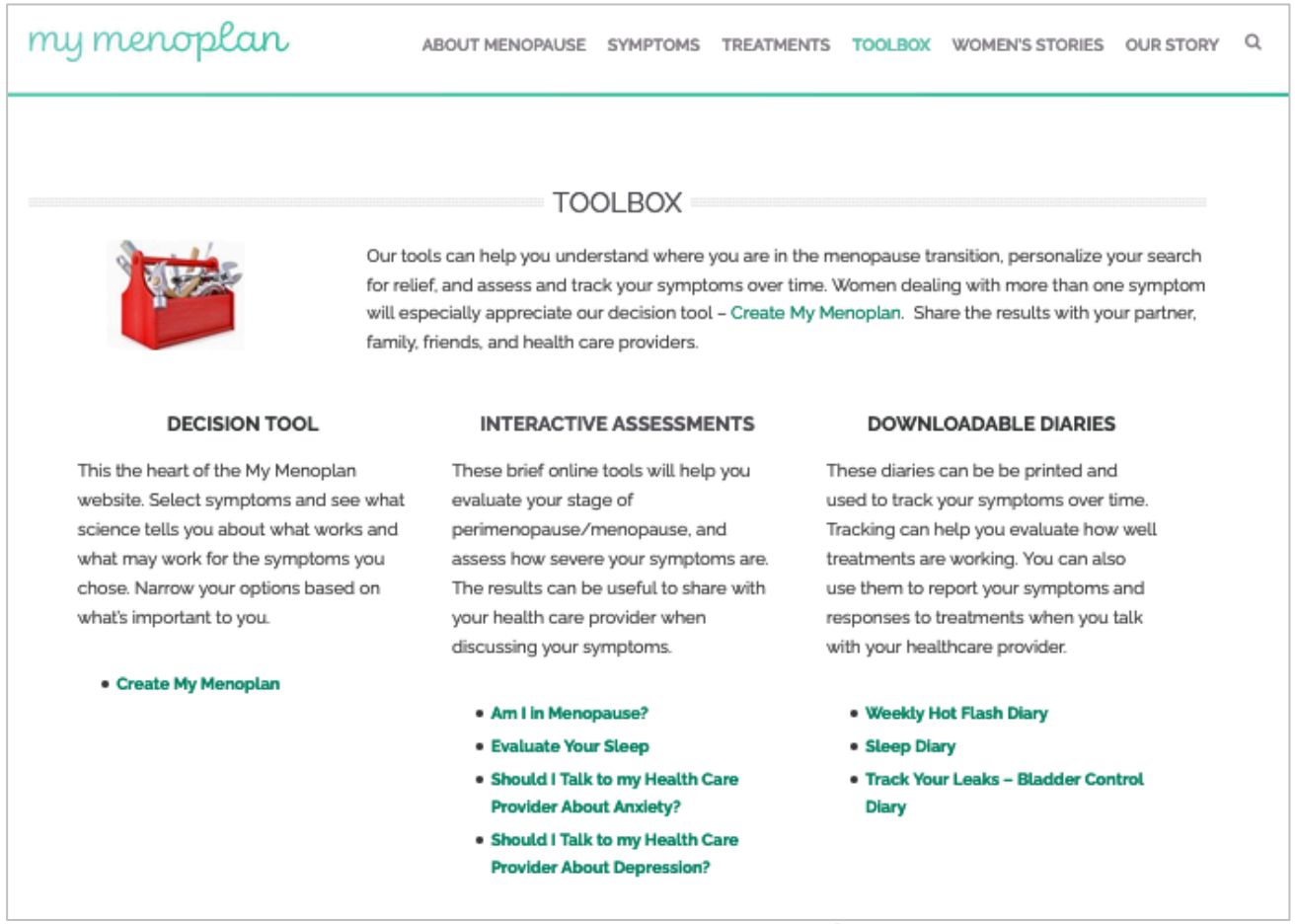

Hyperlink to site https://mymenoplan.org/

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SWAN Menopause FAQs

Hyperlink to site https://www.swanstudy.org/fact-sheets/

SWAN Fact Sheet: Hot Flash Fact Sheet*

"Did you know that:

- Most (up to 80%) of women will have some hot flashes or night sweats as they go through menopause and a few women will have very disruptive hot flashes.
    - o Some women have hot flashes when they are having periods, other women's hot flashes start when their periods stop, other women will have hot flashes both before and after their periods stop.
    - o Hot flashes can be very variable, even in the same woman, in how often they occur and how severe they are.
- Hot flashes differ in severity. Many women have few or mild hot flashes but about 10% of women will have **more than 7 hot flashes a day."**

The Menopause Society MenoNotes

The Menopause Society™
Leading the Conversation

Hyperlink to site https://www.menopause.org/publications/consumer-publications/-i-menonotes-i-

Deciding About Hormone Therapy Use

"Many women experience hot flashes, vaginal dryness, and other physical changes with menopause. For some women, the symptoms are mild and do not require any treatment. For others, symptoms are moderate or severe and interfere with daily activities. Hot flashes improve with time, but some women have bothersome hot flashes for many years. Menopause symptoms often improve with lifestyle changes and nonprescription remedies, but prescription therapies also are available, if needed. Government-approved treatments for bothersome hot flashes include hormone therapy (HT) containing estrogen, as well as a nonhormone medication (paroxetine).

Hormone therapy involves taking estrogen in doses high enough to raise the level of estrogen in your blood in order to treat hot flashes and other symptoms. Because estrogen stimulates the lining of the uterus, women with a uterus need to take an additional hormone, progestogen, to protect the uterus. Women without a uterus just take estrogen."

QUESTIONS?

reeds@uw.edu