Ewha,
Where Change Begins

10 years after WHI
Vasomotor symptoms

이 사 라

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NAMS guideline 2012

Tx. of moderate ~ severe Vasomotor symptom

Primary indication for systemic HT

2010

Every systemic ET and EPT product approved for this indication

2012

Almost all systemic HT products except for ultralow dose E2 transdermal patch have government approval for this indication

- Progestogen alone
  - Also reduces vasomotor Sx
  - But not as effective as estrogen

Vasomotor symptoms

Vasomotor symptoms, hot flashes, hot flushes, night sweat

- VMS : Recurrent, transient episodes of flushing + sensation of warmth to intense heat on the upper body and face

- VMS while sleeping → intense perspiration (night sweats)
- Chills usually after heat → catch cold
- Heart beat increase : ↑ 7-15 beats/min
- Heart rate & skin blood flow : peak within 3 min of onset of hot flash

Hot flash

Hot flash

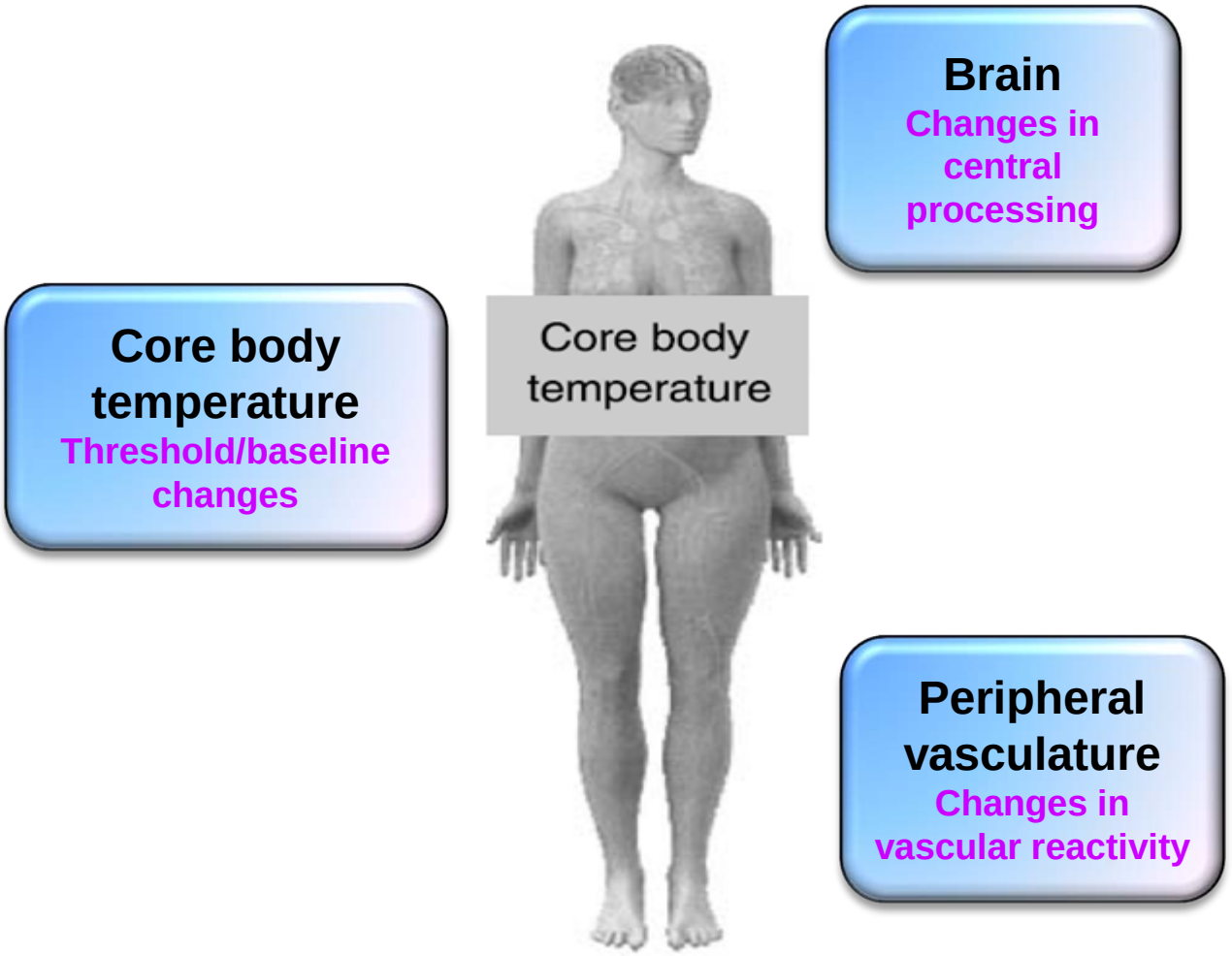
Frequency

- Perimenopause, highest during first 2 years of MP'
- 6mo ~ 2 years / average 3-5 years (~ 10 years)
- *Often recurrence of hot flashes more than 10 years after MP*

Duration

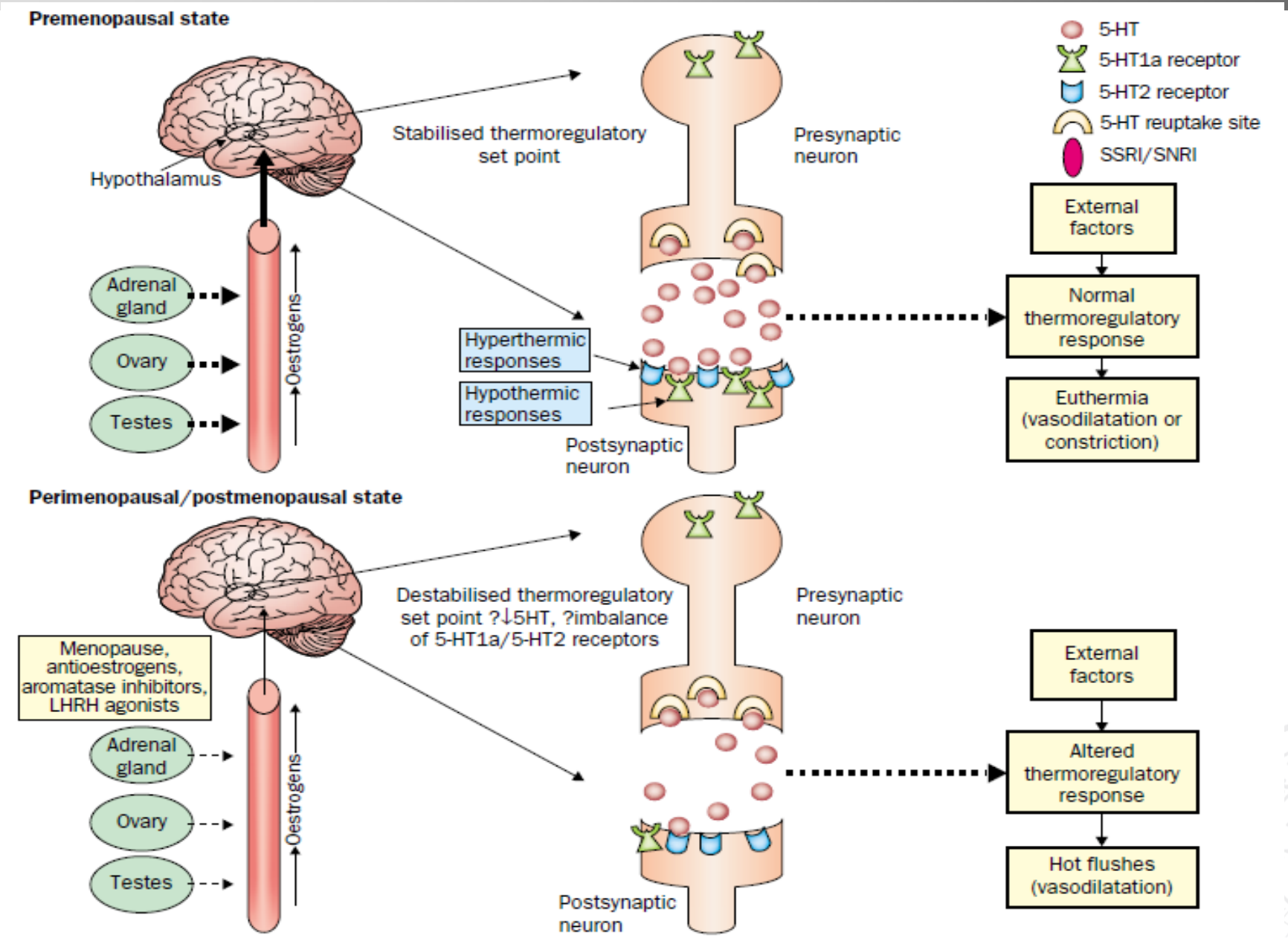
- 1-5 min (ave 4 min), seconds ~ 1 hour
- Finger & toes : peripheral vasodilation → skin temp : ↑ 1~7° C

Pathophysiology
Thermoregulation

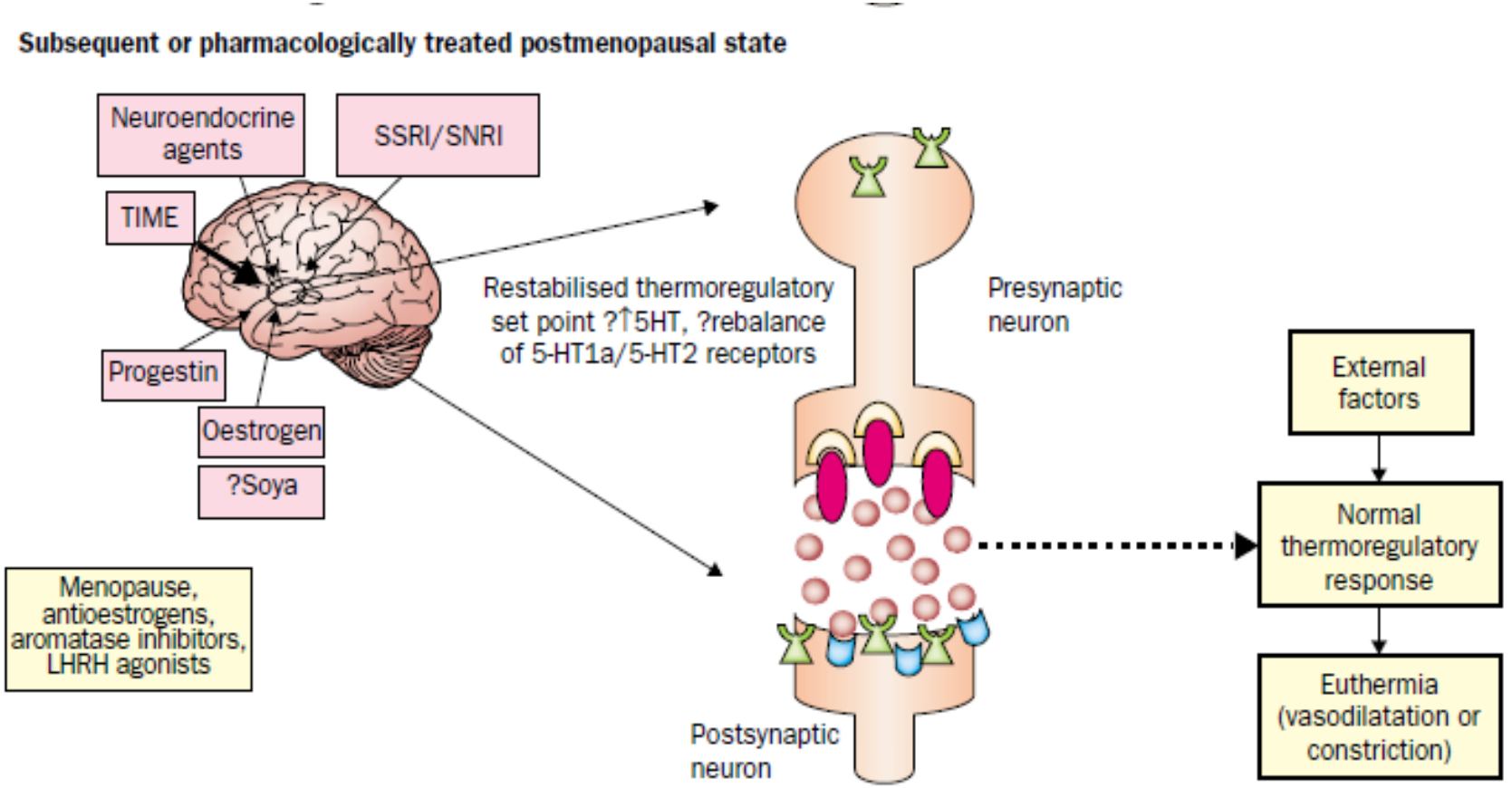


Deecher DC, et al. Arch Womens Ment Health 2007.

Hot flash


Premenopausal state
Hypothalamus
Stabilised thermoregulatory set point
Presynaptic neuron
5-HT
5-HT1a receptor
5-HT2 receptor
5-HT reuptake site
SSRI/SNRI
External factors
Normal thermoregulatory response
Euthermia (vasodilatation or constriction)
Adrenal gland
Ovary
Testes
Oestrogens
Hyperthermic responses
Hypothermic responses
Postsynaptic neuron
Perimenopausal/postmenopausal state
Menopause, antioestrogens, aromatase inhibitors, LHRH agonists
Destabilised thermoregulatory set point ?↓5HT, ?imbalance of 5-HT1a/5-HT2 receptors
Presynaptic neuron
External factors
Altered thermoregulatory response
Hot flushes (vasodilatation)
Adrenal gland
Ovary
Testes
Oestrogens
Postsynaptic neuron

Hot flash



Vered Stearns Lancet 2002

Hot flash – associated problems

- depression, nervousness, agitation, insomnia, and inability to concentrate ??? MP ? Hot flush?
- Anxiety - 증가시 hot flush 많다
- Depression – new onset

SWAN study) 42 ~52 years women

Psychosocial Factors	OR (95% CI)
Baseline anxiety (summed score ≥4)	3.10 (2.33, 4.12)
Baseline depressive symptom score ≥16	1.62 (1.22, 2.15)

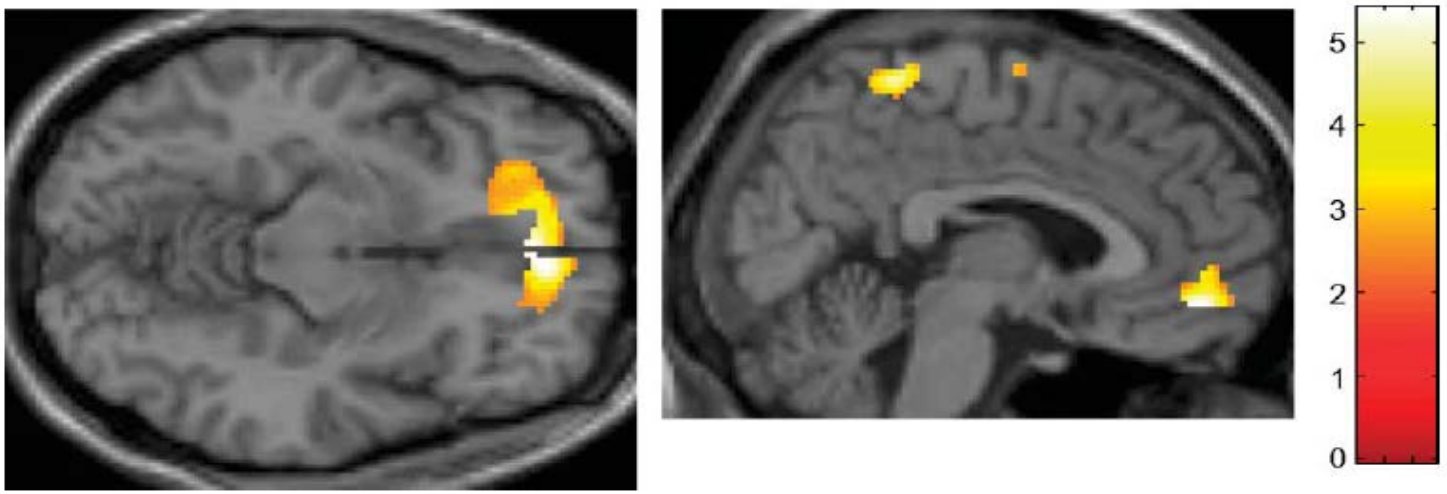
Gold EB, et al. Am J Public Health 2006.

- Impaired memory function
- impaired cognitive function (?)

Hot flash – associated problems

- impaired cognitive function

Intervention	**E2 patch 0.05 mg/d,**12 weeks (n=26)	**Placebo patch** (n=26)



➔significant activation in the inferior frontal cortex and parietal regions during completion of the verbal recall task (at T ≥ 3.4, P < 0.001)

➔ Women with **baseline hot flushes** and had greater cognitive benefit with ET.
Also, women **with improvement in hot flush** had greater cognitive benefit with ET.
Cognitive benefit was Not associated with sleep problems or its improvement.

Joffe H, et al. Menopause 2006.

Vasomotor symptoms

Prevalence

- ✓ ~25% of US women experience sufficient discomfort
- ✓ 22–63% in Asia
- ✓ 54% (Choi, et al. 2003) (61% in women with MP symptoms)

Risk factor for hot flashes

Panel 2: **Risk factors for hot flushes**

Low concentration of circulating oestrogen
Low bodyweight
Little or no exercise
Cigarette smoking
African-American origin
Low socioeconomic status
Low educational status
Menopause at a young age
Abrupt menopause
  Surgically induced
  Chemotherapy induced
  Radiation induced
  Drug induced

Vasomotor symptoms – in Men

Men with Prostate cancer

- Hot flushes are also common - androgen deprivation
- 70% of men surgical orchiectomy
  (30–40% of these patients - major discomfort)
- 80% : neoadjuvant HT before radical prostatectomy

- Estrogen treatment of prostate ca. – 1/3 patients also have hot flash
  (less intense, shorter)

Vered Stearns Lancet 2002

Management of VMS

- No treatment is needed unless the hot flashes are bothersome.

- Treatment for ***Cure ? Relief ?***
- Hot flush typically stop without treatment, then when ?
- Placebo effect in studies of hot-flash treatments is as high as 50%

Management of VMS

- Treatment for VMS should be based on

✓ The ***severity*** of the symptoms

Hot flash severity
- Mild = feeling of warmth that is barely noticeable,
- Moderate = hot flashes which are very apparent and with some perspiration
- severe = intense feeling of heat with perspiration.

✓ Assessment of treatment-related risks

✓ Woman's personal attitudes about menopause and medication

- for reducing their symptoms?
- for complete amelioration of symptoms?

Management of VMS

	Population	Hot flush reduction		Adverse effects
		Agent	Placebo	
Oestrogen[79]	PM	50–100%	. .	Thromboembolic events, gallbladder disease; endometrial adenomatous hyperplasia, fluid retention, breast discomfort, and irregular bleeding in women; feminisation, including breast enlargement in men.
Progestagen[80–82]	BC, PC	71–90%	21–26%	Thromboembolic events, bloating, weight gain, nausea, vomiting, vaginal bleeding.
Soya[83–90]	PM, BC	35–45%	25–38%	Constipation, bloating and flatulence, dyspepsia, nausea, vomiting, allergic reactions.
Black cohosh[91]	BC	27–28%	30–32%	Dyspepsia, nausea, vomiting, and other gastrointestinal disturbances; high-dose headache, dizziness, hypotension, visual disturbances.
Vitamin E[92]	BC	25%	22%	Rare reversible nausea, vomiting, diarrhoea, breast enlargement, fatigue, weakness
Clonidine[93,94]	BC on tamoxifen	37–41%	20–27%	Drowsiness, dry mouth, constipation, hypotension.
SSRIs[95–98]	PM, BC	34–65%	27–38%	Dry mouth, nausea, decreased appetite, constipation, difficulty sleeping.

BC=breast cancer survivors. PC=patients with prostate cancer. PM=postmenopausal women. SSRIs=selective serotonin reuptake inhibitors.

Vered Stearns Lancet 2002

Management of VMS

Agent	Number of studies in meta-analysis	Duration of treatment	Mean difference in number of hot flushes per day*
Oral 17-β-oestradiol and progestagen	5	12 to 24 weeks	−16·8 (−23·4 to −10·2)†
Transdermal 17-β-oestradiol	6	11 to 12 weeks	−22·4 (−35·9 to −10·4)†
Gabapentin	2	8 to 12 weeks	−2·05 (−2·80 to −1·30)
SSRI or SNRI (paroxetine, venalfaxine, citalopram)	6	4 weeks to 12 months	−1·13 (−1·70 to −0·57)
Clonidine	10	4 weeks 8 weeks	−0·95 (−1·44 to −0·47) −1·63 (−2·76 to −0·05)
Red-clover isoflavones	6	12 weeks to 12 months	−0·44 (−1·47 to 0·58)
Soy isoflavones	11	4 to 6 weeks 6 months 12 months	−1·15 (−2·33 to 0·03) −0·97 (−1·82 to −0·12) −1·22 (−2·02 to −0·42)

*Compared with control. †Per week. SSRI=selective serotonin reuptake inhibitors. SNRI=serotonin-norepinephrine reuptake inhibitors.

Table: **Overview of treatments for hot flushes that have been included in recent meta-analyses[2,14]**

Vered Stearns Lancet 2007 June

Management of VMS

Table 6. Suggested options to manage VMS
Enhance relaxation with meditation, yoga, massage, or a leisurely lukewarm bath.
Exercise regularly to increase fitness, maintain a healthy weight, and promote better, more restorative sleep
Keep cool by dressing in layers, using a fan, and sleeping in a cool room
Maintain a ***healthy body weight***
Don't smoke
Try paced respiration (deep, slow, abdominal breathing) when a hot flash starts
Avoid perceived personal hot flash triggers (eg. Hot drinks, caffeine, spicy foods, alcohol, emotional reactions) although studies among large numbers of women do not support an association

Management of VMS

Table 6. Suggested options to manage VMS
Try nonprescription therapies (eg. Soy foods/isoflavones, black cohosh, or vitamin E) : many are available for *mild* hot flashes but have not been found very effective
Consider HT (the only government-approved treatment) or nonestrogen prescription drugs (eg. Progestogens, clonidine [Catapres-TTS®, Dixarit®], venlafaxine [Effexor®], paroxetine[Paxil®], gabapentin[Neurontin®], for *moderate to severe* hot flashes

VMS – nonhormonal : black cohosh

Cochrane Database Syst Rev. 2012 Sep 12;9:CD007244. doi: 10.1002/14651858.CD007244.pub2.

Black cohosh (Cimicifuga spp.) for menopausal symptoms.

Leach MJ, Moore V.

AUTHORS' CONCLUSIONS:

There is currently insufficient evidence to support the use of black cohosh for menopausal symptoms. However, there is adequate justification for conducting further studies in this area. The uncertain quality of identified trials highlights the need for improved reporting of study methods, particularly with regards to allocation concealment and the handling of incomplete outcome data. The effect of black cohosh on other important outcomes, such as health-related quality of life, sexuality, bone health, night sweats and cost-effectiveness also warrants further investigation.

Management of VMS – Hormone

- ***Estrogen / Estrogen + Progestogen therapy***

- ET /EPT
- Estrogen-based therapies have been used for several decades and decrease hot flashes by up to 90%

- EPT is more effective than E alone.

- Therapeutic standard for moderate ~ severe MP symptoms

- Individualize consistent with treatment goals, benefit, risk

Management of VMS – Hormone

- ***Progestogen***

- Progestogen only for hot flush : off label
- P is also highly effective, reducing hot flash by 80%

- Oral MPA, depot MPA, megestrol acetate – demonstrated efficacy
- EE = MPA for the treatment of VMS
- 2/3 transdermal P trial - no benefit for placebo

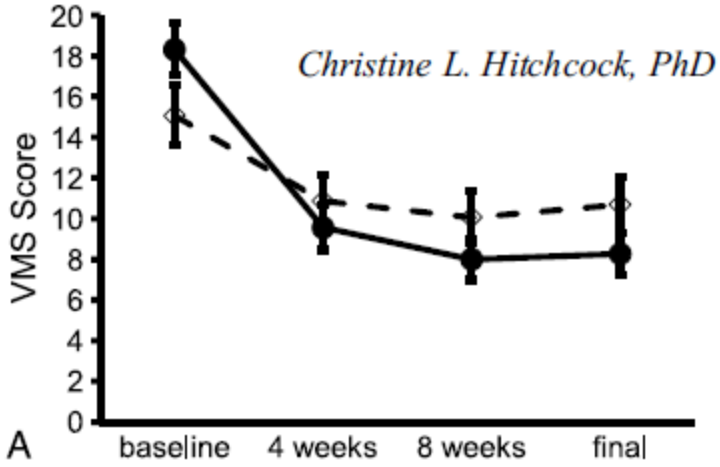
- Breast cancer risk - only for short- term use can be resonable

Management of VMS – Hormone

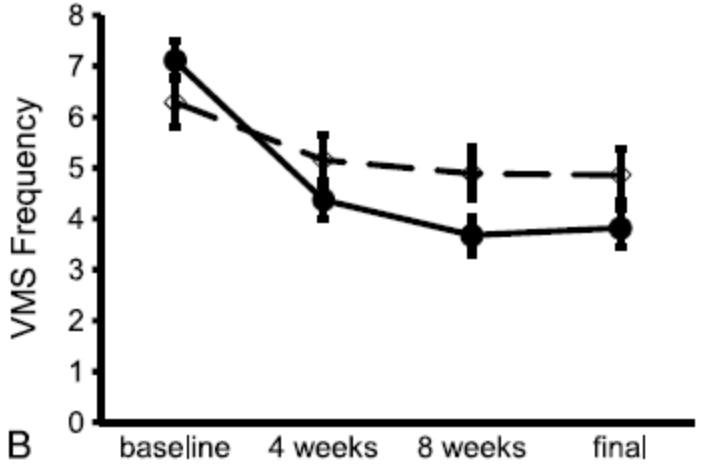
Menopause: The Journal of The North American Menopause Society
Vol. 19, No. 8, pp. 886-893
DOI: 10.1097/gme.0b013e318247f07a

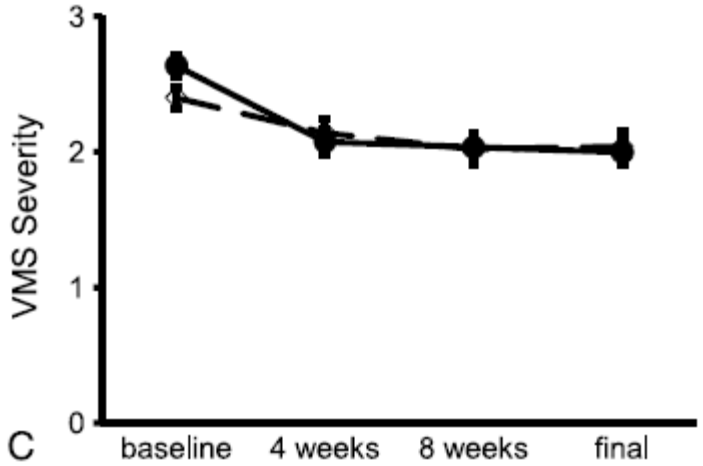
Oral micronized progesterone for vasomotor symptoms—a placebo-controlled randomized trial in healthy postmenopausal women

Christine L. Hitchcock, PhD and Jerilynn C. Prior, BA, MD



- RCT : progesterone (300 mg/d HS) / placebo
- 133 healthy women with VMS, 44~62 years
- Mean VMS score of 17.0 (10.4) at run-in (VMS frequency 6.8 [3.2] episodes/d)





Management of VMS – Hormone

- ***Combined oral contraceptives***

- Perimenopausal women who require hot flash relief and contraception
- Low dose combined estrogen-progestin OC
- Only for healthy women who do not smoke or contraindications

Management of VMS – SSRI, SNRI

Selective serotonin receptor inhibitor (SSRI)

- Fluoxetine (20mg/d)
- Paroxetine (12.5mg/d /25mg/d) or (50mg/d)
- Venlafaxine (37.5~75mg/d)

Serotonin-Norepinephrine reuptake inhibitor (SNRI)

➔ Options for women with hot flashes but not candidates of HT

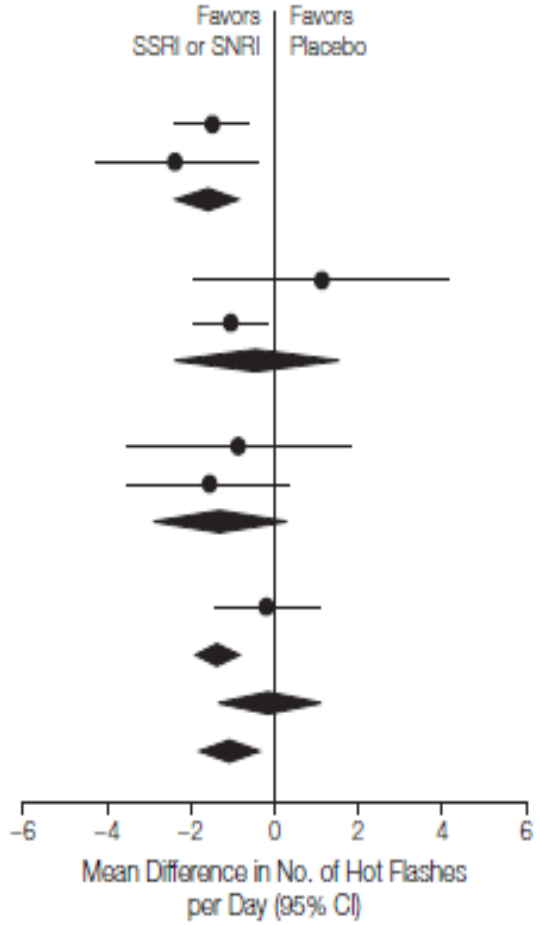
➔ No research for long-term use of SSRI, SNRI for hot flashes in non-depressed population once the drugs are withdrawn

Caution is urged

Management of VMS – SSRI, SNRI

Figure 2. Trials of Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Source	Dose	No. of Participants	Duration of Trial	Quality	Mean Difference (95% CI)
Paroxetine Trials					
Stearns et al,[29] 2003	12.5 or 25 mg/d*	165	6 wk	Good	−1.52 (−2.36 to −0.69)
Stearns et al,[30] 2005	10 or 20 mg/d	151	4 wk	Fair	−2.43 (−4.43 to −0.42)
Combined					−1.66 (−2.43 to −0.89)
Venlafaxine Trials					
Evans et al,[22] 2005	75 mg/d*	80	12 wk	Fair	1.10 (−1.94 to 4.14)
Loprinzi et al,[31] 2000	37.5 or 75 mg/d*†	167	4 wk	Good	−1.09 (−1.99 to −0.18)
Combined					−0.49 (−2.40 to 1.41)
Fluoxetine Trials					
Loprinzi et al,[32] 2002	20 mg/d	81	4 wk	Fair	−0.90 (−3.78 to 1.98)
Suvanto-Luukkonen et al,[23] 2005	20 mg/d‡	100	3 mo	Fair	−1.60 (−3.63 to 0.43)
Combined					−1.37 (−3.03 to 0.29)
Citalopram Trials					
Suvanto-Luukkonen et al,[23] 2005	20 mg/d‡	100	3 mo	Fair	−0.20 (−1.45 to 1.05)
Trials With SERM Use Combined§					−1.40 (−1.97 to −0.82)
Trials Without SERM Use Combined‖					−0.17 (−1.41 to 1.07)
All Trials Combined					−1.13 (−1.70 to −0.57)



EWHA WOMANS UNIVERSITY

Nelson HD JAMA 2006

Management of VMS – SSRI, SNRI

SSRI & Tamoxifen

- CYP2D6 - for both metabolism
- Effectiveness ↓ tamoxifen in breast ca

- ***Serum level of tamoxifen : ↓ 24~64% after 4 weeks of paroxetine treatment***

- Paroxetine is the greatest negative effect

Management of VMS – SSRI, SNRI

SSRI - Precaution

- *Rapid relief* on hot flashes(2-4 weeks) ➔ attractive !
  whereas not rapid for depression (6-8weeks)

- SE) *nausea, sexual dysfunction, drowsy* – should mention
- Nausea – dose related, subside within 2 weeks of start
- Drowsy – nighttime taking
- Weight gain, blurred vision – rare

Management of VMS – SSRI, SNRI

SNRI

- Weight loss (due to anorexia) → preferred *to overweight women*

SSRI, SNRI – stopping : caution

- *Don't stop taking abruptly* ➔ headache, anxiety