

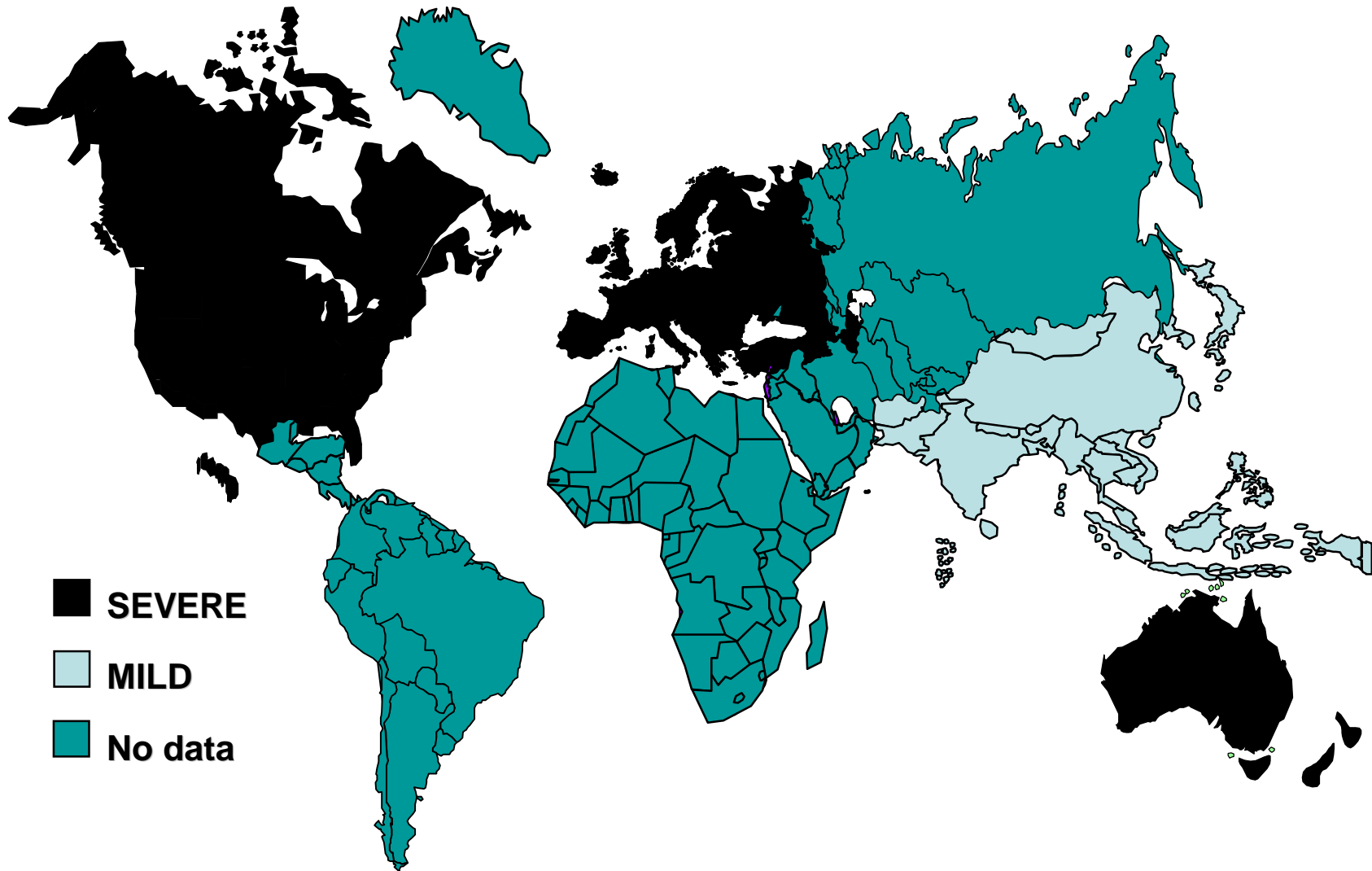
Non Hormonal Approach to Management of Hot Flashes

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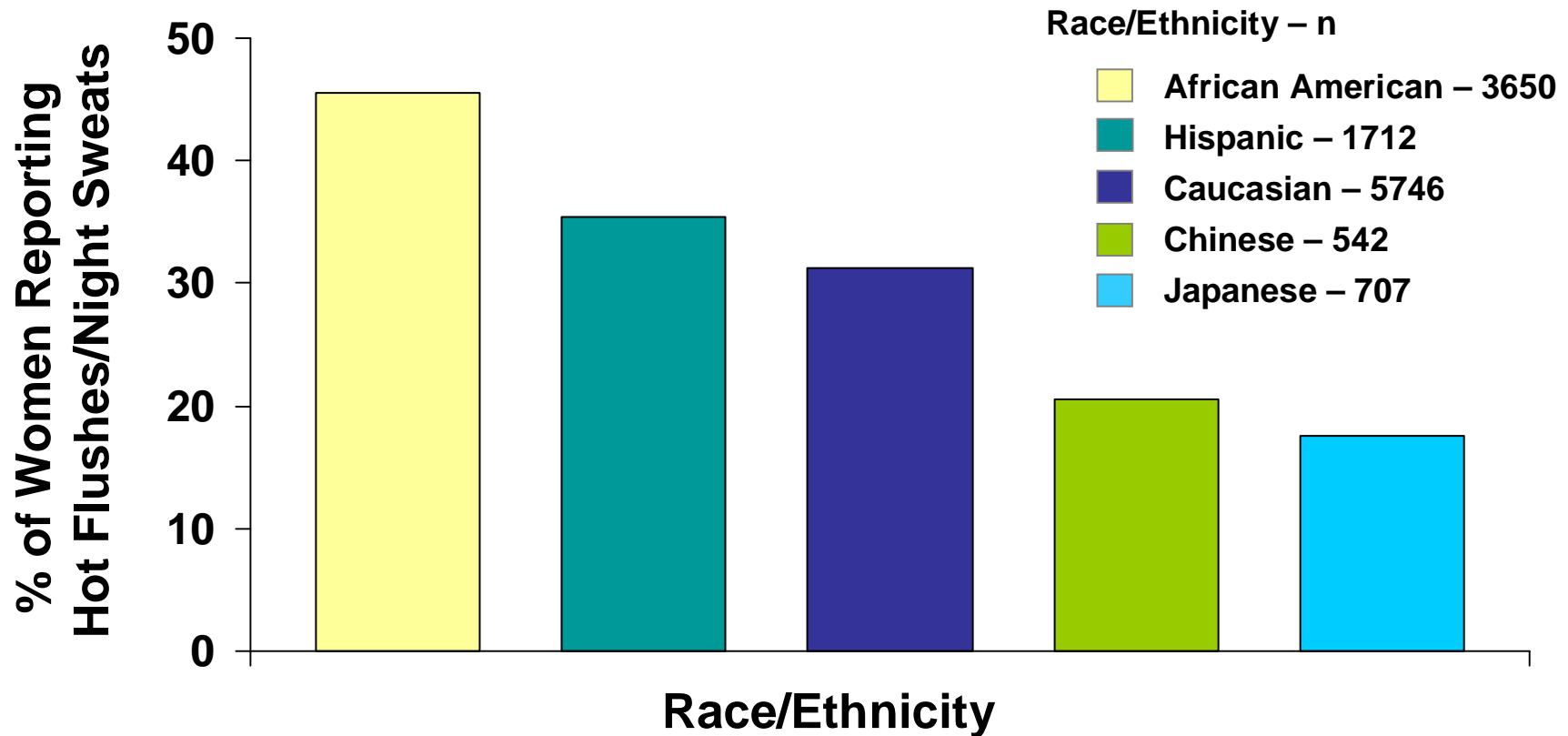


Menopause Related Symptoms



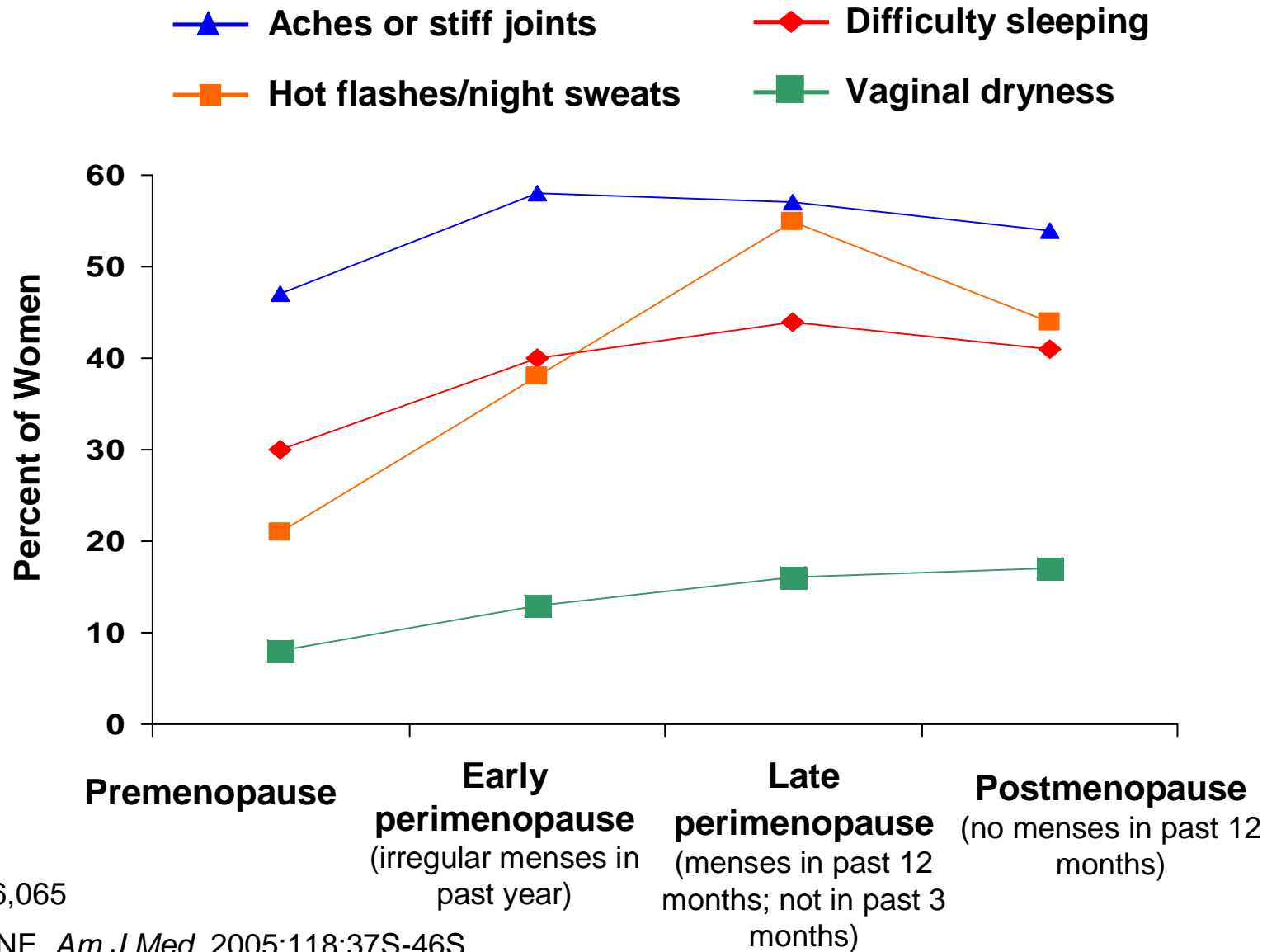
SWAN Study: Reported Prevalence of Vasomotor Symptoms in Perimenopausal Women

Ages 40 to 55 Years



n = 12,357; SWAN = Study of Women's Health Across the Nation.
Gold EB, et al. *Am J Epidemiol.* 2000;152:463-73.

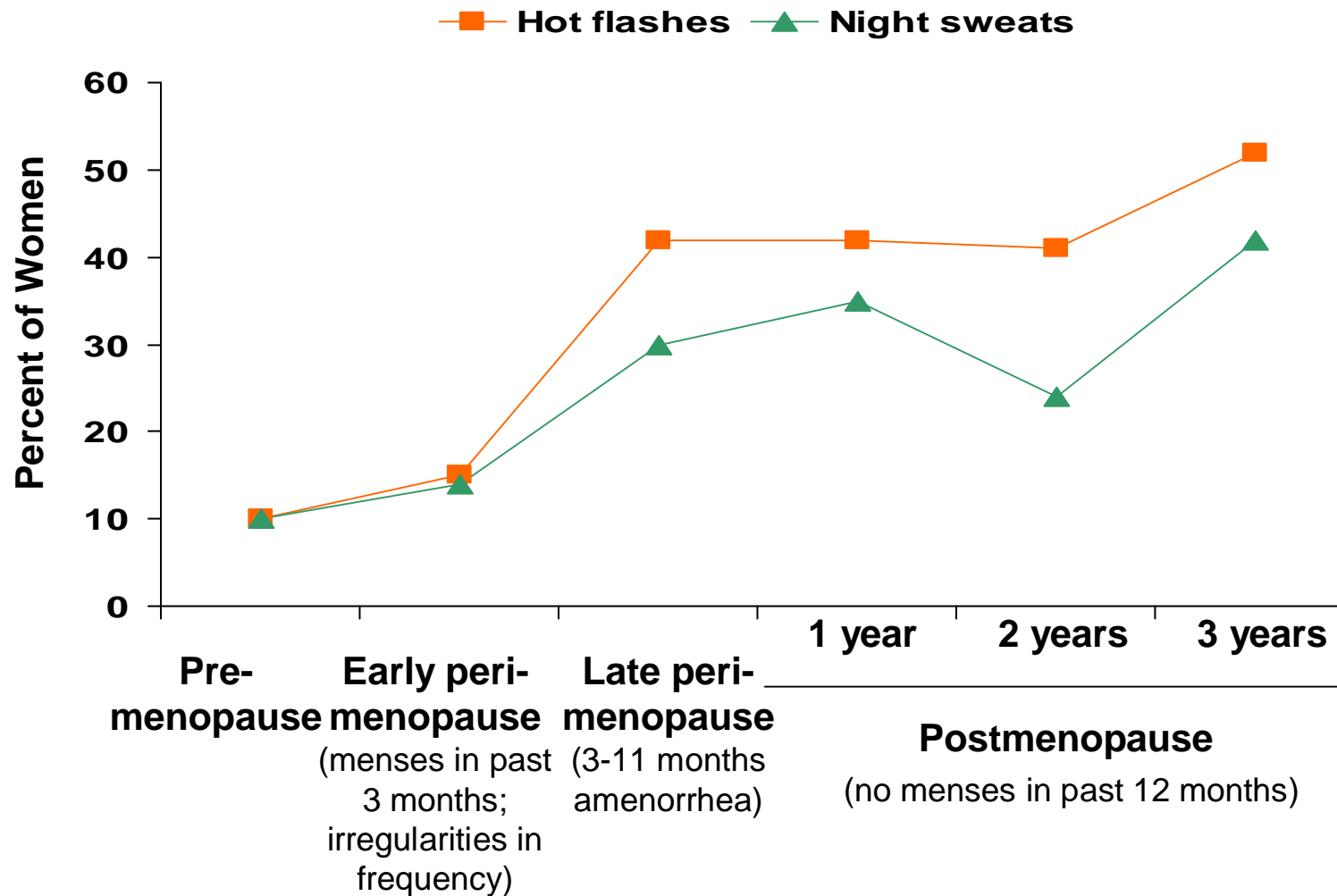
Study of Women's Health Across the Nation: Symptom Reporting



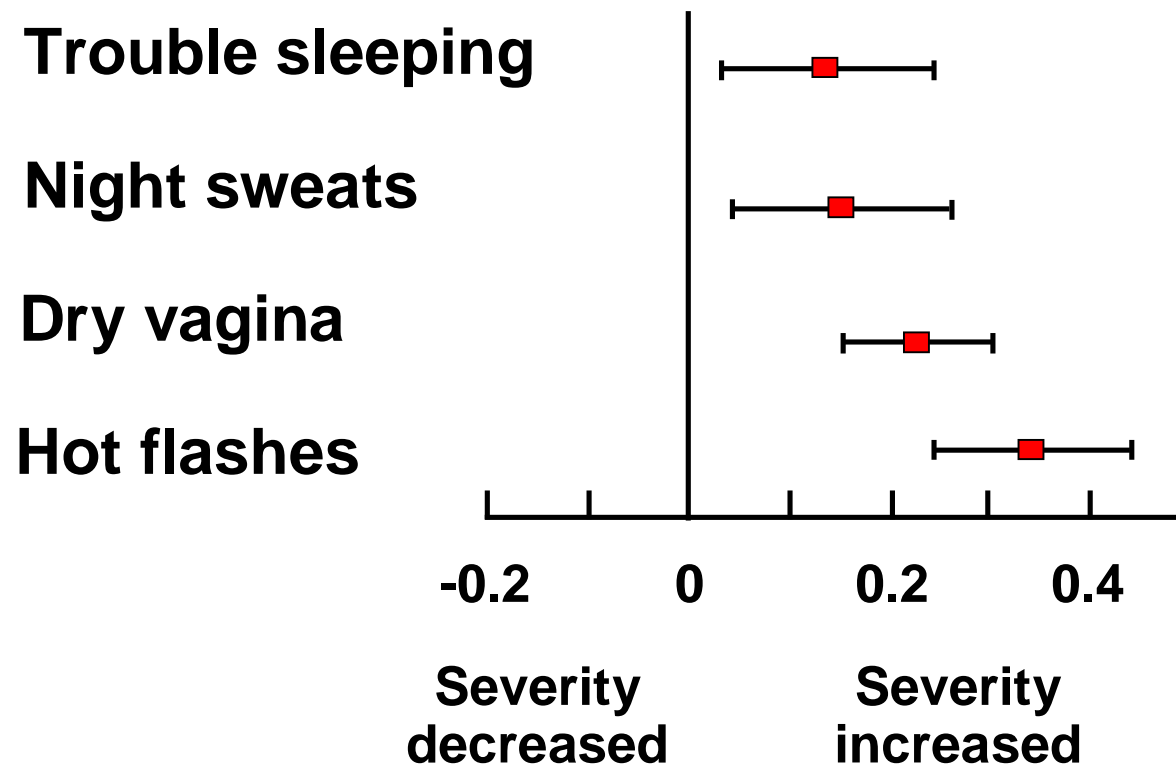
N=16,065

Avis NE. *Am J Med.* 2005;118:37S-46S.

Vasomotor Symptoms Across the Menopausal Transitions



Symptoms With Increasing Severity in Late Perimenopause and Postmenopause



No other symptoms were significantly changed with menopausal status

Defining Severity of Vasomotor Symptoms

Mild

- **Sensation of heat without sweating**
-

Moderate

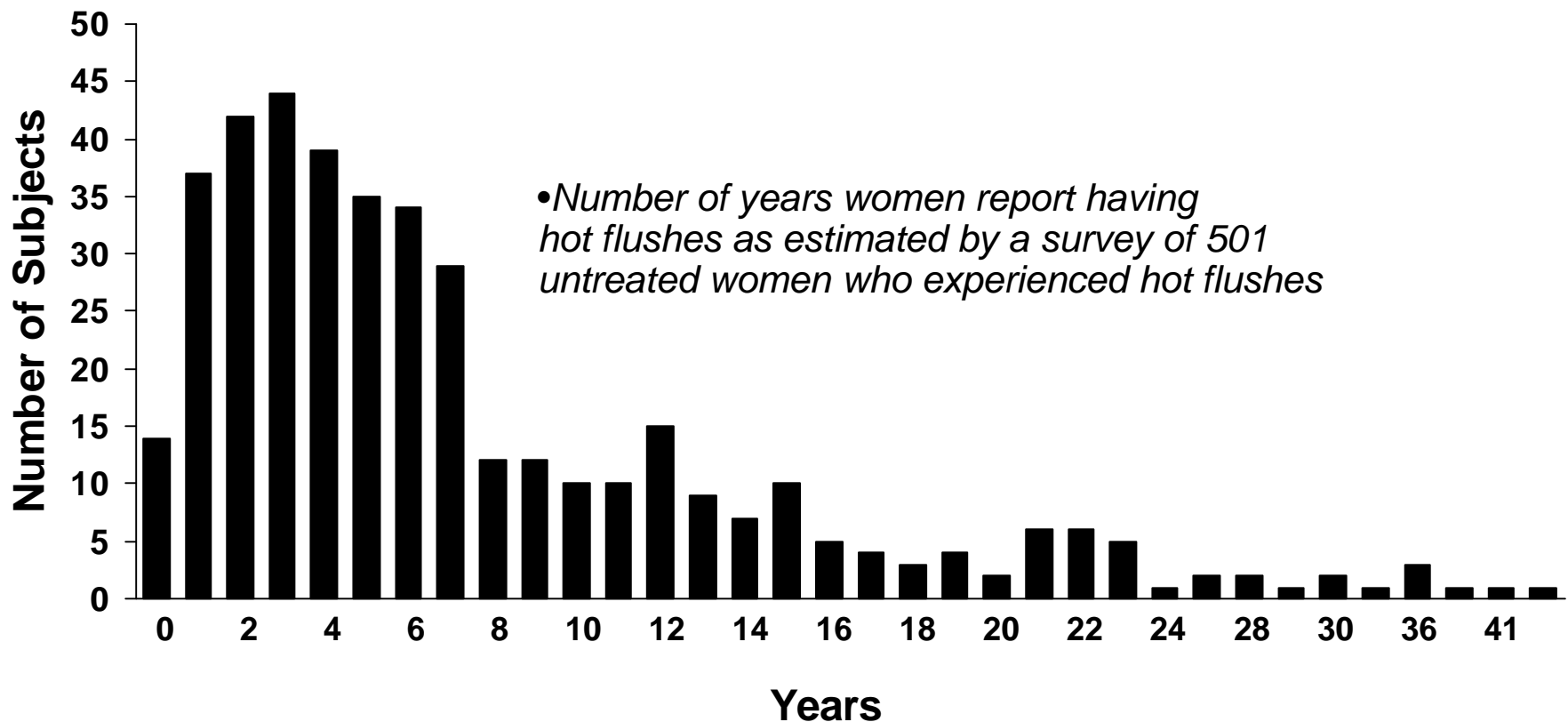
- **Sensation of heat with sweating**
 - **Able to continue activity**
-

Severe

- **Sensation of heat with sweating**
- **Resulting in cessation of activity**

Hot Flushes May Continue Years After Menopause

Ages 29 to 82 Years



Mean age of natural menopause was 49.5 years; mean age of surgical menopause was 43.7 years.
Kronenberg F. *Ann NY Acad Sci.* 1990;592:52-86. Used with permission.

Hot Flush Mechanisms

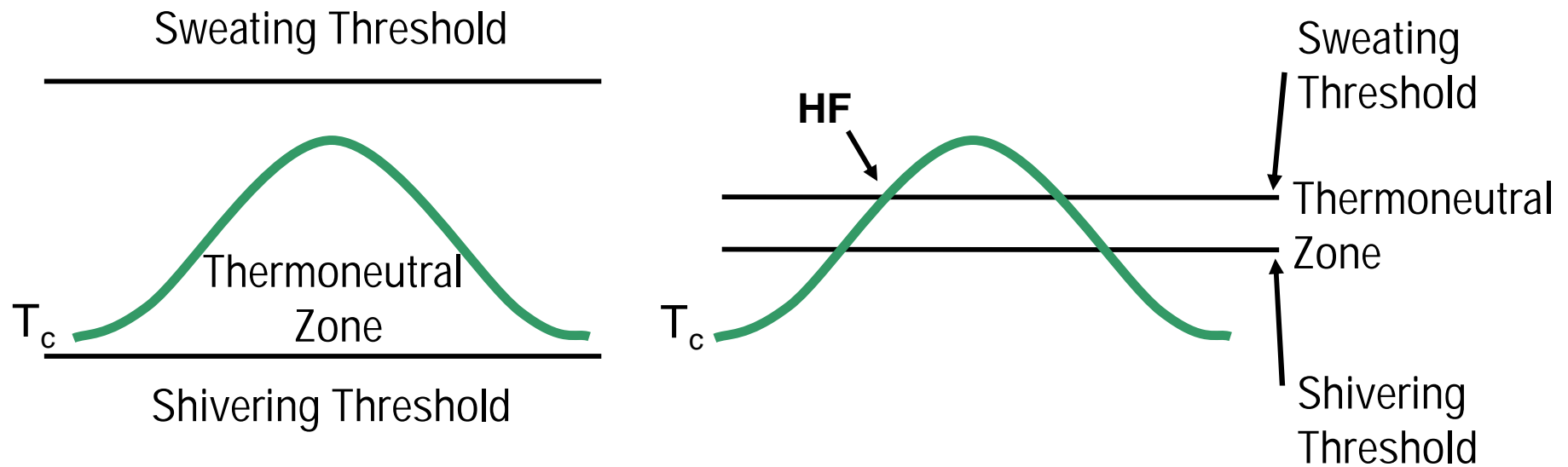
- Hot flushes and shivering may result from small fluctuations in core body temperature superimposed on an extremely narrow thermoneutral zone*
- Hot flushes occur when core body temperature rises above the upper (sweating) threshold
- Shivering occurs when core body temperature falls from the elevated level to a level below the lower threshold of the thermoneutral zone

*Zone in which neither sweating nor shivering occurs.
Freedman RR, Blacker CM. *Fertil Steril.* 2002;77:487-90.

Pathophysiology of Hot Flashes

Asymptomatic

Symptomatic



T_c = core body temperature; HF = hot flash.
Freedman RF. *Semin Reprod Med.* 2005;23:117-25.

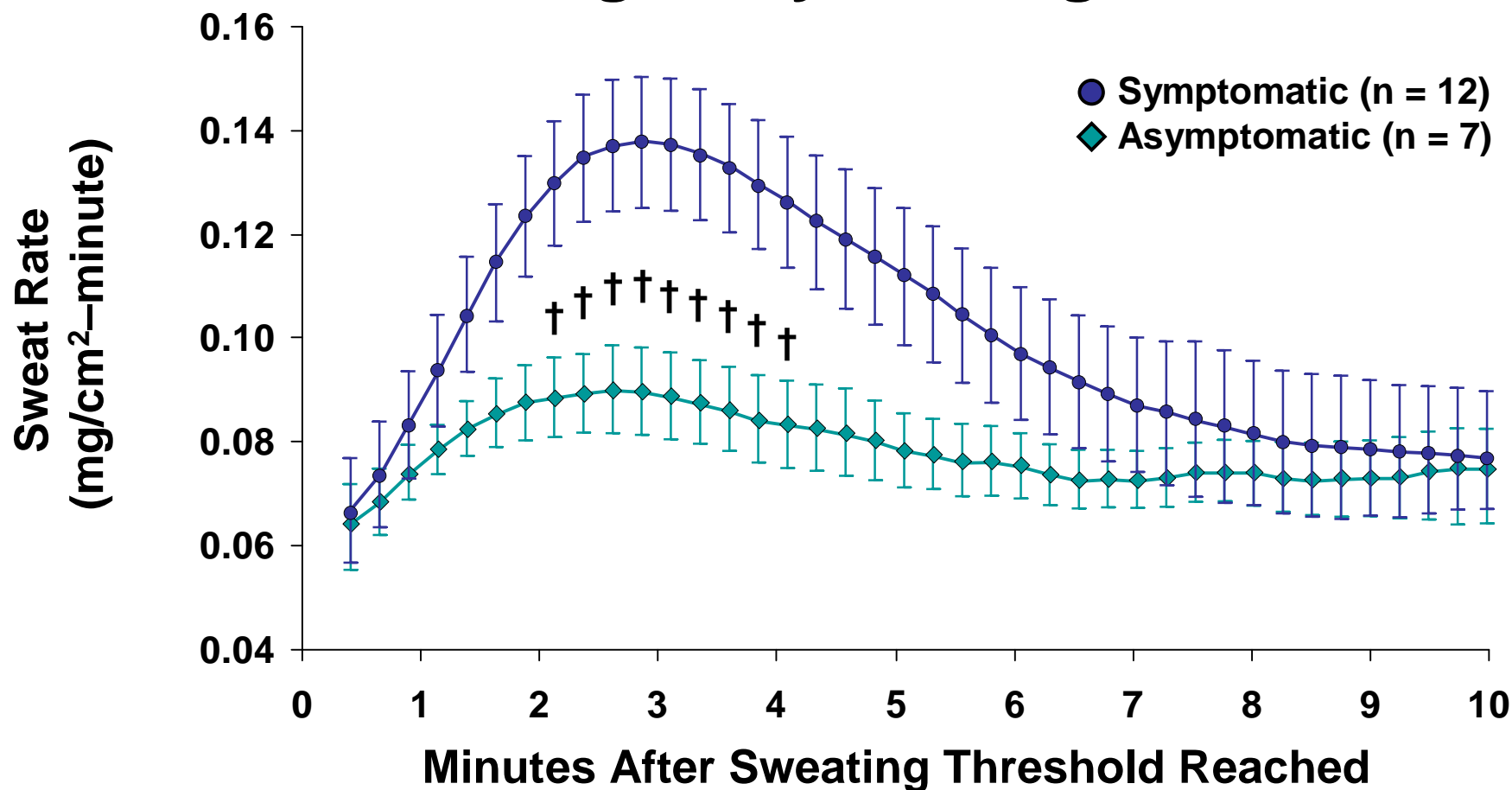
Body Temperature and Time to Reach Sweating Threshold in Symptomatic and Asymptomatic Postmenopausal Women

	Substance Administered	Symptomatic (n = 12)	Asymptomatic (n = 7)
Core body temperature (°C)	Placebo	37.1 ± 0.07*	37.4 ± 0.05†
	Clonidine	37.3 ± 0.09	37.2 ± 0.03
Skin temperature (°C)	Placebo	36.0 ± 0.2	36.5 ± 0.2
	Clonidine	36.2 ± 0.2	36.5 ± 0.2
Time to sweating threshold (min)	Placebo	84.7 ± 9.1*	130.4 ± 9.9
	Clonidine	132.0 ± 10.6*	149.4 ± 10.2

**P* < .05 vs asymptomatic women; †*P* < .05 vs clonidine.

Adapted from Freedman RR, Dinsay R. *Fertil Steril.* 2000;74:20-3.

Sweat Rates in Symptomatic and Asymptomatic Postmenopausal Women During Body Heating*



*Room temperature increased from 23°C to 26°C and subjects' torsos were covered with 2 circulating water pads at 42°C.

† $P < .05$.

Freedman RR, Dinsay R. *Fertil Steril.* 2000;74:20-3.

Estrogen and Neurotransmitter Systems

Serotonergic System

↑ Serotonin uptake capacity¹

↑ Tryptophan availability to brain²

Modulates serotonin receptor expression³

↓ Age-related decline in serotonergic responsivity⁴

Estrogen



↓ Monoamine oxidase activity^{7,8}

Catecholaminergic System

↑ Dopamine release⁵

↑ Norepinephrine release⁶

¹Sherwin BB, Suranyi-Cadotte BE. *Biol Psychiatry*. 1990;28:339-48.

²Aylward M. *IRCS J Int Res Commun Med Sci*. 1973;1:30-4.

³Mize AL, et al. *Neuroendocrinology*. 2001;73:166-74.

⁴van Amelsvoort TAMJ, et al. *Psychoneuroendocrinology*. 2001;26:493-502.

⁵Ohtani H, et al. *Brain Res*. 2001;900:163-8.

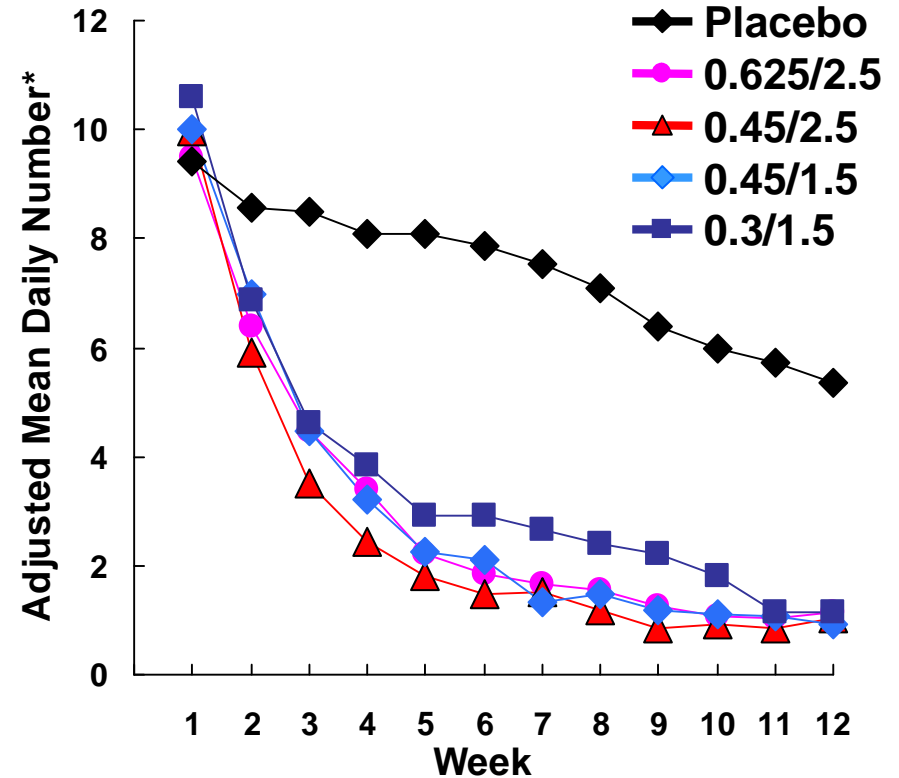
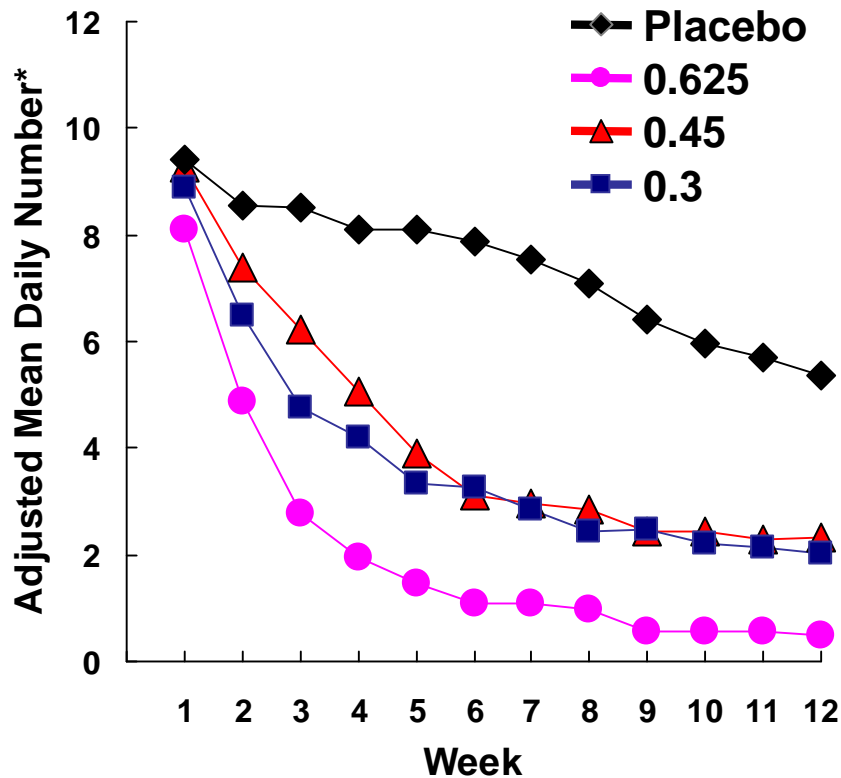
⁶Paul SM, et al. *Brain Res*. 1979;178:499-505.

⁷Luine VN, et al. *Brain Res*. 1975;86:293-306.

⁸Klaiber EL, et al. *J Clin Endocrinol Metab*. 1971;33:630-8.

Women's HOPE Study

Change in Number of Hot Flushes Over 12 Weeks (n = 241)



*Adjusted for baseline.

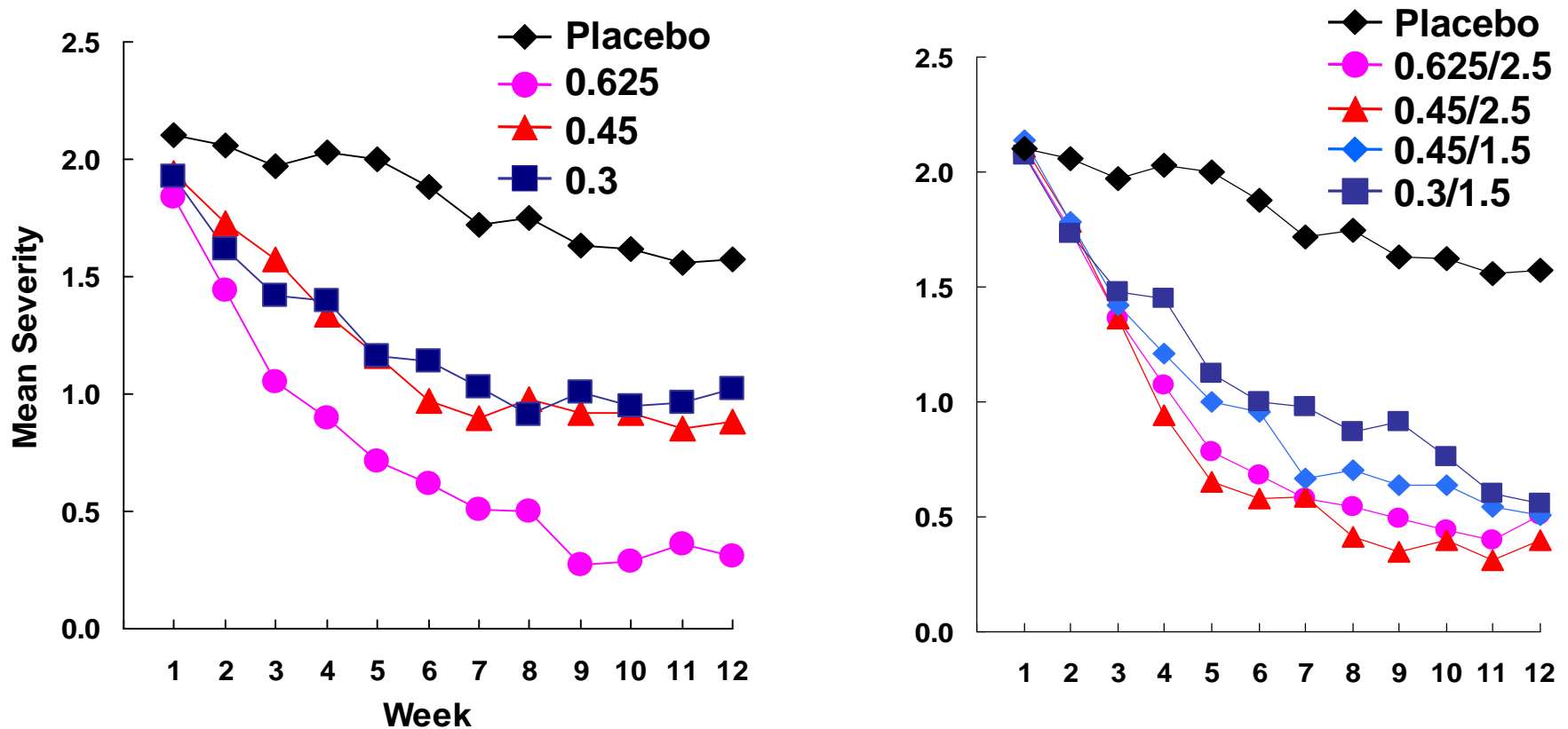
Mean hot flushes at baseline = 12.3 (range 11.3–13.8).

Analyses included women who recorded taking study medication and had at least 7 moderate-to-severe flushes/week or at least 50 flushes per week at baseline.

Utian WH, et al. *Fertil Steril.* 2001;75:1065-79. Used with permission.

Women's HOPE Study

Changes in Severity of Hot Flashes Over 12 Weeks (n = 241)

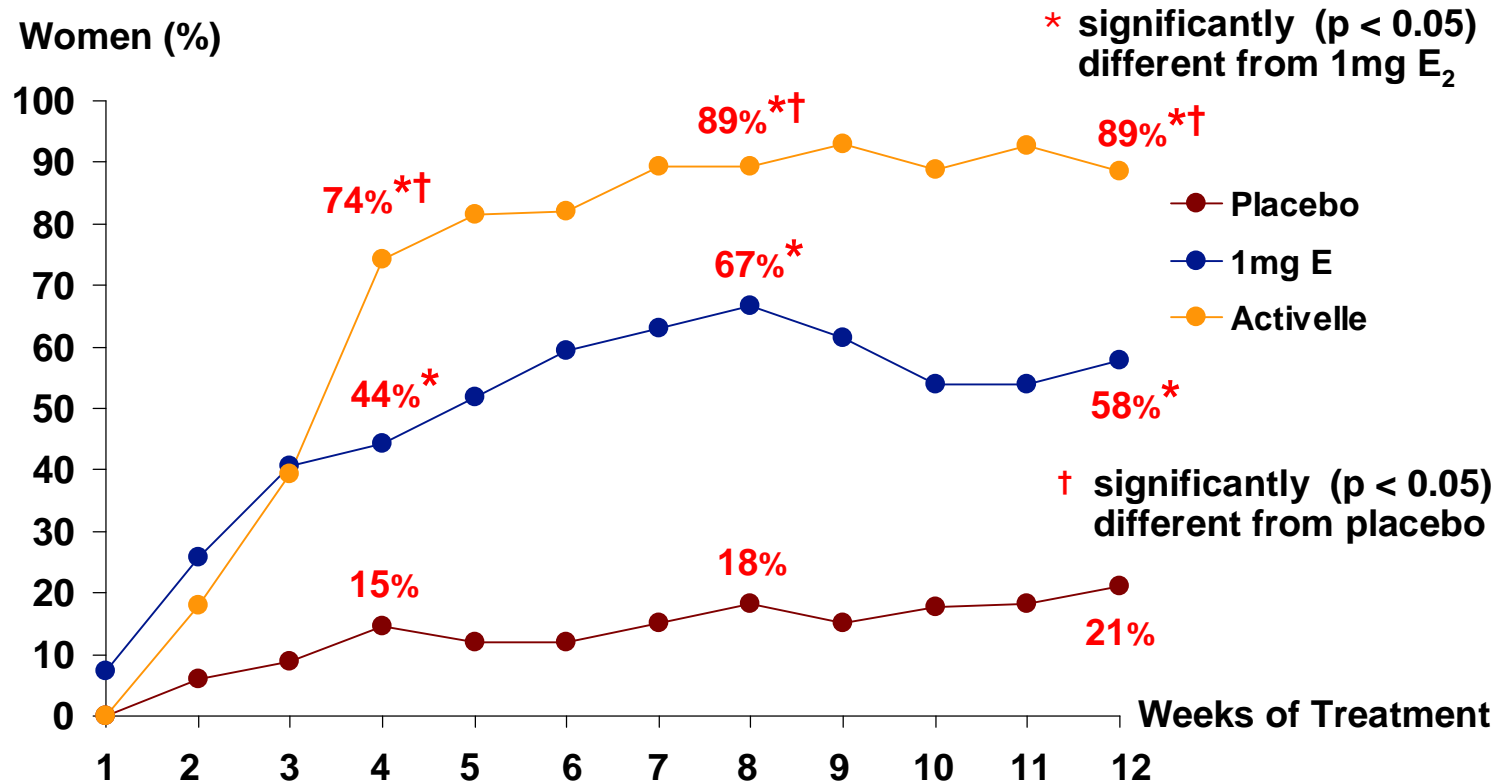


Hot flash severity: 1 = mild, 2 = moderate, 3 = severe. Mean hot flash severity at baseline = 2.3 (range 2.2–2.4).
 EE = Efficacy-evaluable population included women who recorded taking study medication and had at least 7 moderate-to-severe flushes/week or at least 50 flushes per week at baseline.

Utian WH, et al. *Fertil Steril*. 2001;75:1065-79. Used with permission.

Hot Flush Reduction

% of women achieving 90-100% reduction in hot flushes weekly weighted score (HFWS) with E₂, E₂/NETA and Placebo



Progestins for the Treatment of Vasomotor Symptoms

Progestin	N	Dose	Efficacy
<i>MPA Oral</i>	27	20 mg/d	25.9%–34.5% ↓ in hot flushes
	21	100 mg BID	
<i>MPA Depot</i>	71	500 mg + 40 mg megestrol	67%–80% ↓ in hot flushes
	15	500 mg weekly	95% ↓ in hot flushes
	42	150 mg	69% ↓ in hot flushes
<i>Megestrol</i>	97	20 mg/d	85% ↓ vs 21% placebo

Sleep Disturbances Are Associated With Estrogen Loss

- Many women report sleep complaints around the time of the menopause^{1,2}**
- ET improves women's subjective reports of sleep quality, even in women who are free of menopausal symptoms³**
- Compared with nonusers, ET users experience increased time in REM sleep and reduced time awake⁴**

¹Oldenhave A, et al. *Am J Obstet Gynecol.* 1993;168:772-80.

²Polo-Kantola P, et al. *CNS Drugs.* 2001;15:445-52.

³Polo-Kantola P, et al. *Am J Obstet Gynecol.* 1998;178:1002-9.

⁴Antonijevic IA, et al. *Am J Obstet Gynecol.* 2000;182:277-82.

ET May Restore Normal Sleep Electroencephalogram (EEG)

Improvements in Sleep EEG Patterns After Open-label Treatment With Estradiol

Sleep Parameter	Baseline (mean \pm SD)	With Estrogen (mean \pm SD)*
Time awake in first 2 cycles (minutes)	20.1 \pm 5.9	11.9 \pm 5.4
Time in REM sleep in first 2 cycles (minutes)	39.4 \pm 4.5	50.0 \pm 4.3

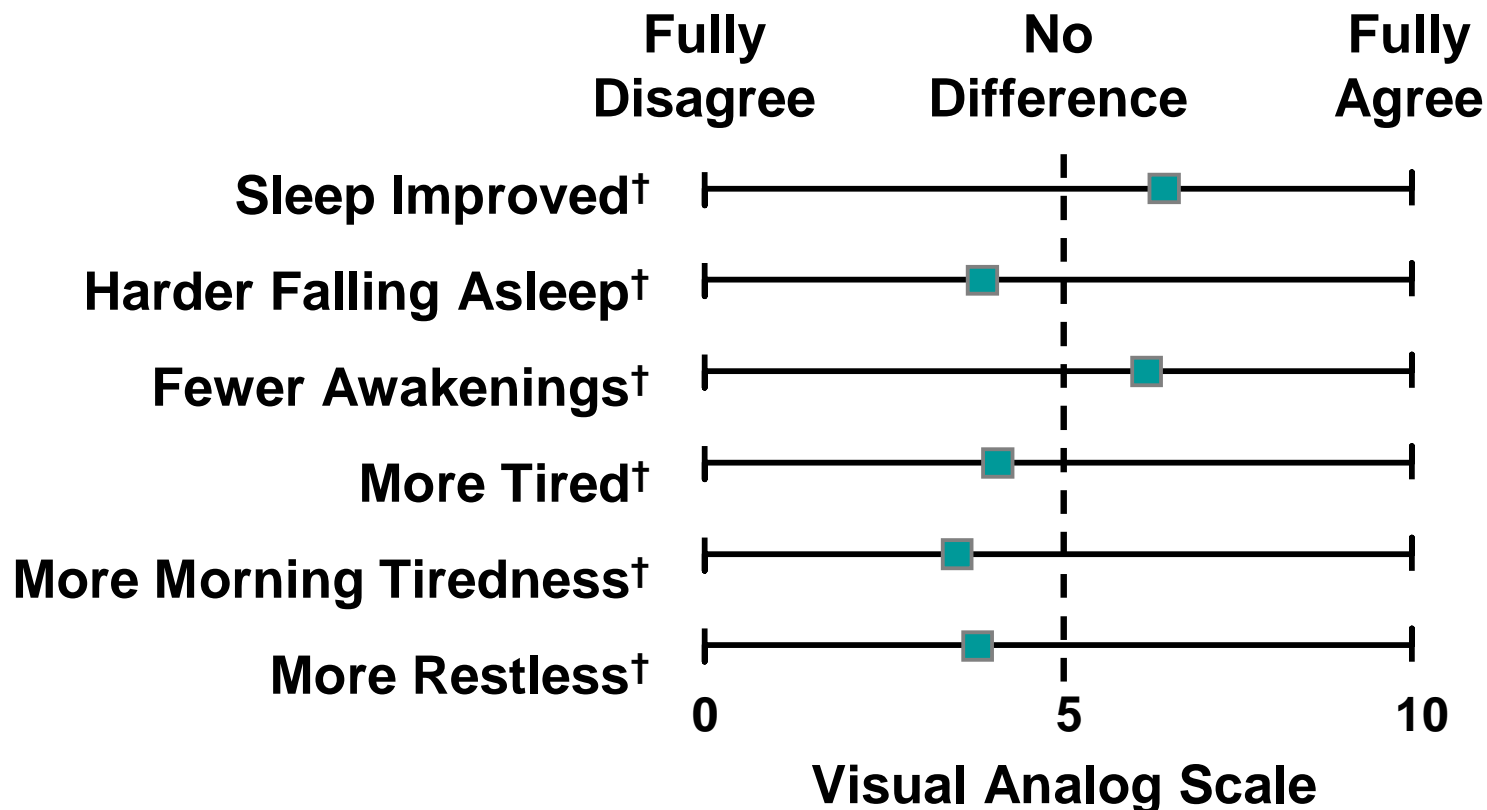
n = 11 postmenopausal women; mean age, 55 years.

* $P < .05$ for all parameters.

Adapted from Antonijevic IA, et al. *Am J Obstet Gynecol.* 2000;182:277-82.

Postmenopausal Women Report Improved Sleep After 3 Months of ET

Mean Age, 56 Years*



*Age range, 47 to 65 years; n = 63.

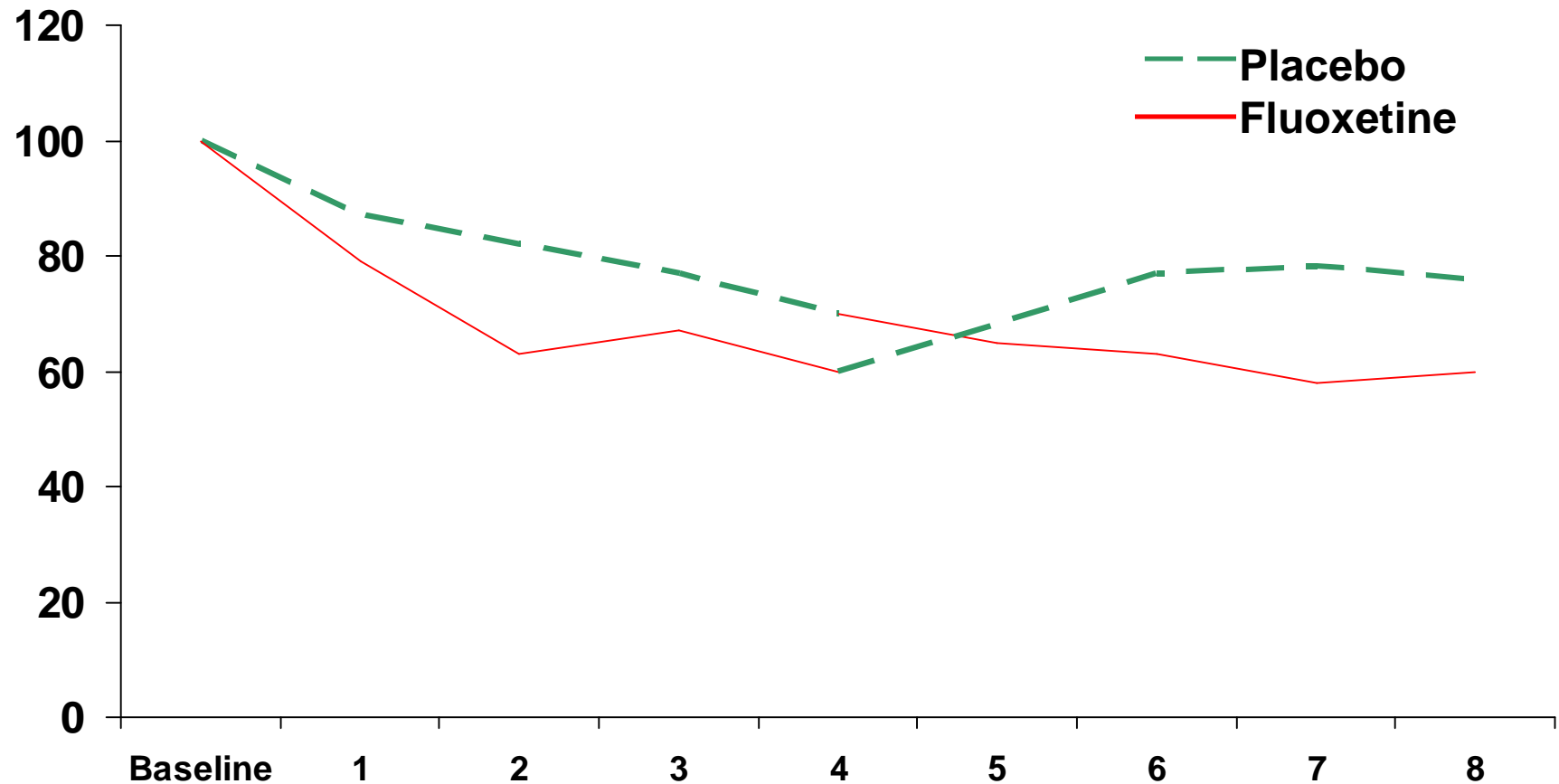
† $P < .001$ compared with placebo.

Adapted from Polo-Kantola P, et al. When does estrogen replacement therapy improve sleep quality? *Am J Obstet Gynecol.* 1998;178:1002-9. Used with permission from Mosby, Inc.

Nonhormonal Prescription Therapies: Fluoxetine

- Randomized, double-blind, placebo-controlled, 8-week crossover trial (two 4-week periods) to evaluate the efficacy of fluoxetine (20 mg/day) for vasomotor symptoms**
- N = 81 women with a history of breast cancer or perceived high risk of breast cancer**
 - Could be on stable doses of tamoxifen or raloxifene**
- At least 14 hot flushes per week**
- 20% improvement compared with placebo ($P = .02$)**

Mean Hot Flash Score Changes from Baseline Fluoxetine versus Placebo

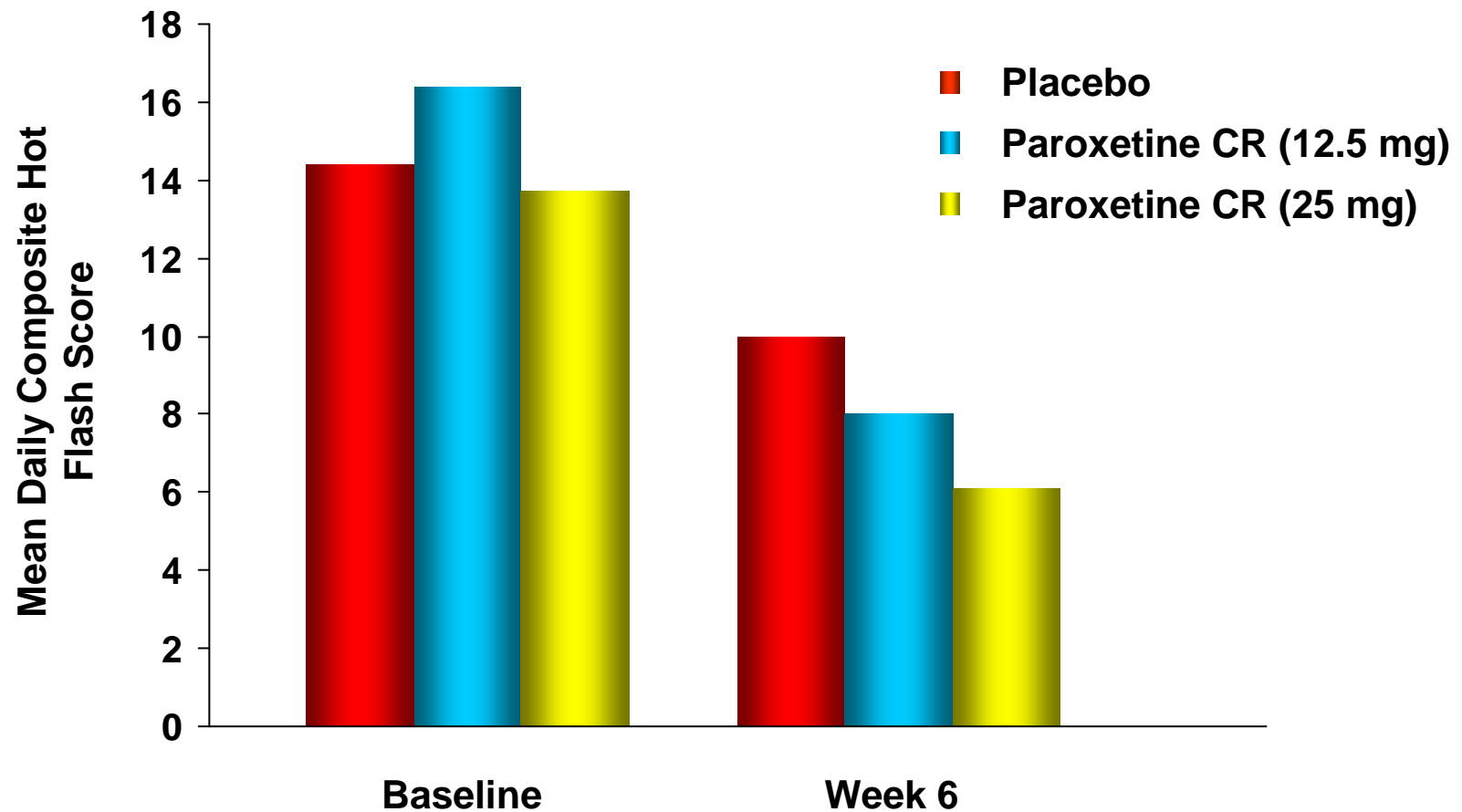


Nonhormonal Prescription Therapies: Paroxetine

- 165 women, 18 years of age or older
- Experiencing 2 to 3 hot flushes per day

Doses (n)	Median Reduction in Hot Flush Composite Score
<i>12.5 mg (51)</i>	<i>62.2% (P = .007)</i>
<i>25 mg (58)</i>	<i>64.6% (P = .03)</i>
<i>Placebo (56)</i>	<i>37.8%</i>

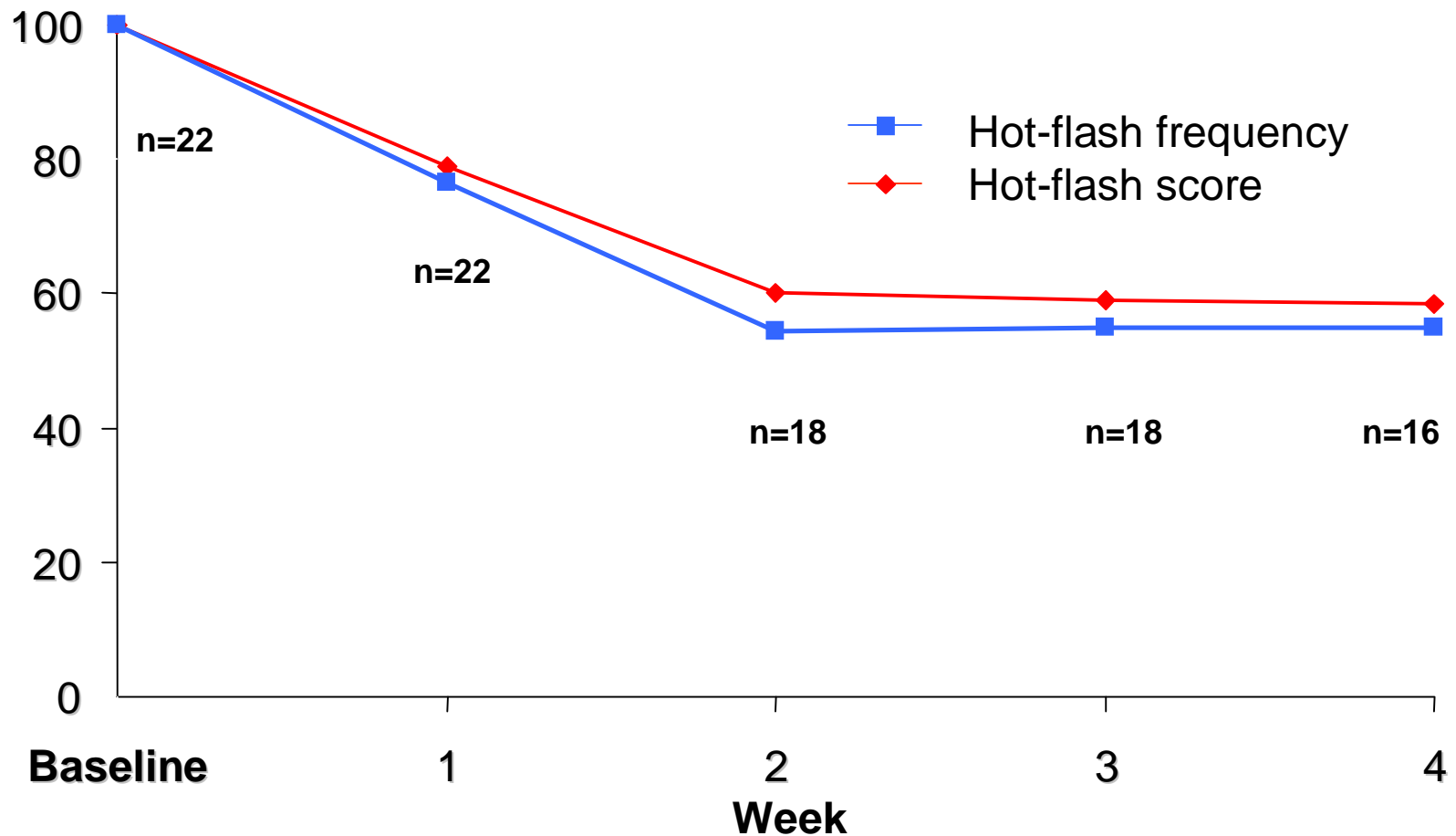
Paroxetine Improves Hot Flashes



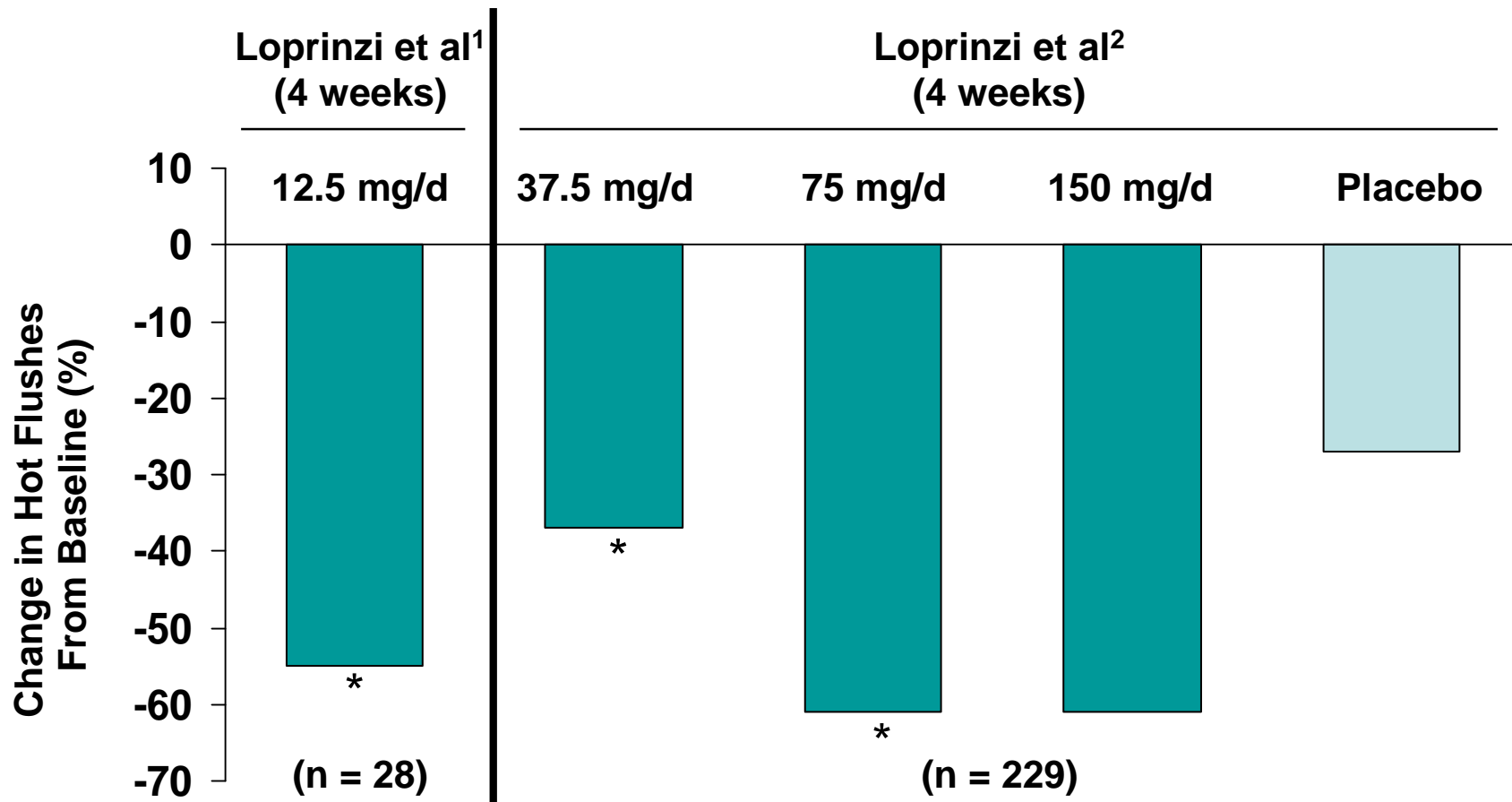
N=160

Stearns V, et al. *JAMA*. 2005;289:2827-2834.

Reduction of Hot Flashes in Patients Receiving Mirtazapine



Nonhormonal Prescription Therapies: Venlafaxine

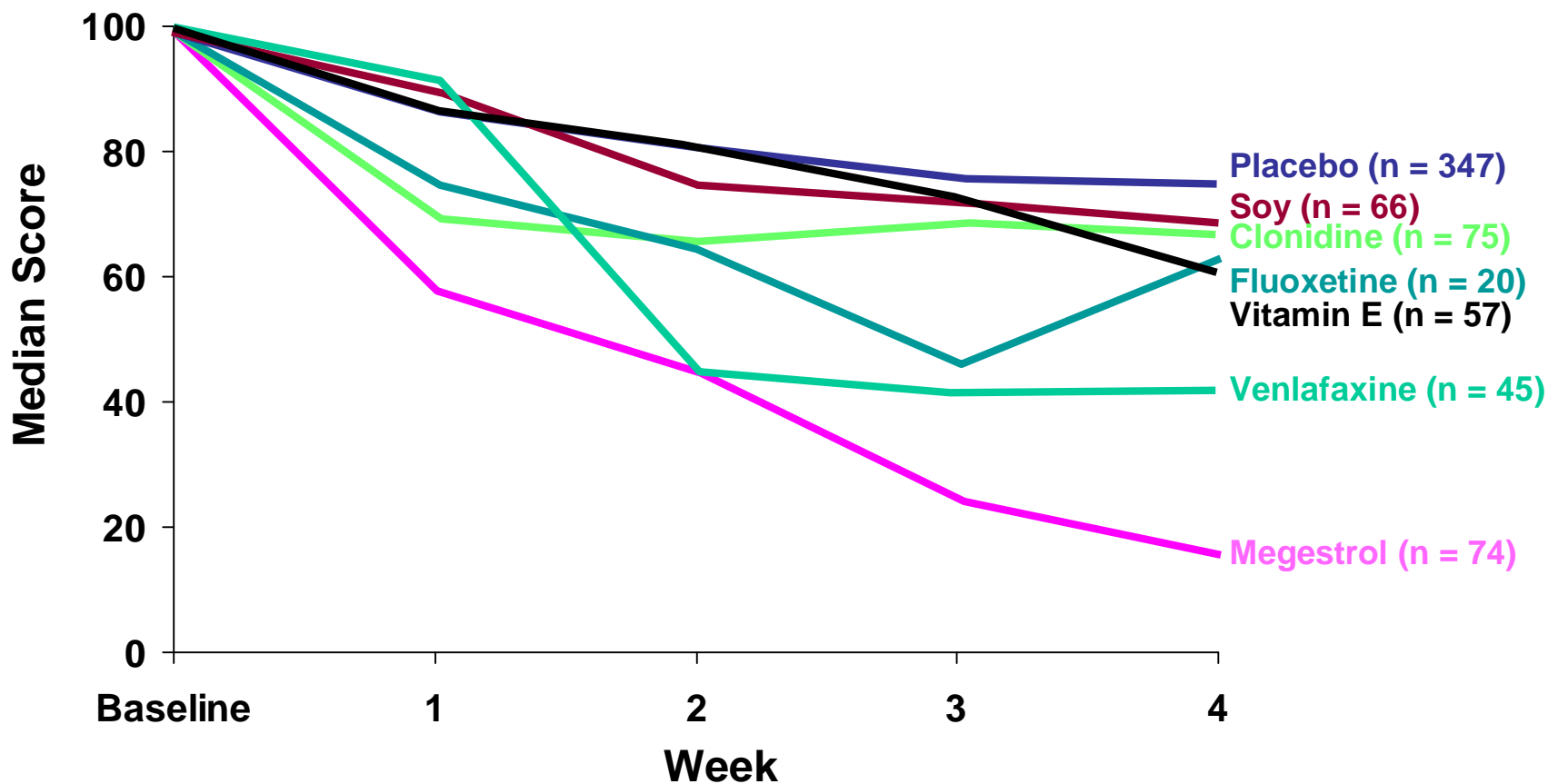


* $P < .05$.

Schober CE, Ansani NT. *Ann Pharmacother.* 2003;37:1703-7.

¹Loprinzi CL, et al. *J Clin Oncol.* 1998;16:2377-81; ²Loprinzi CL, et al. *Lancet.* 2000;356:2059-63.

Clinical Trials of Median Hot Flush Score Reduction in Breast Cancer Patients



NOTE: These data are not from head-to-head trials.
Loprinzi CL, et al. *Lancet Oncol.* 2001;2:199-204.

Desvenlafaxine Succinate SR for Vasomotor Symptoms

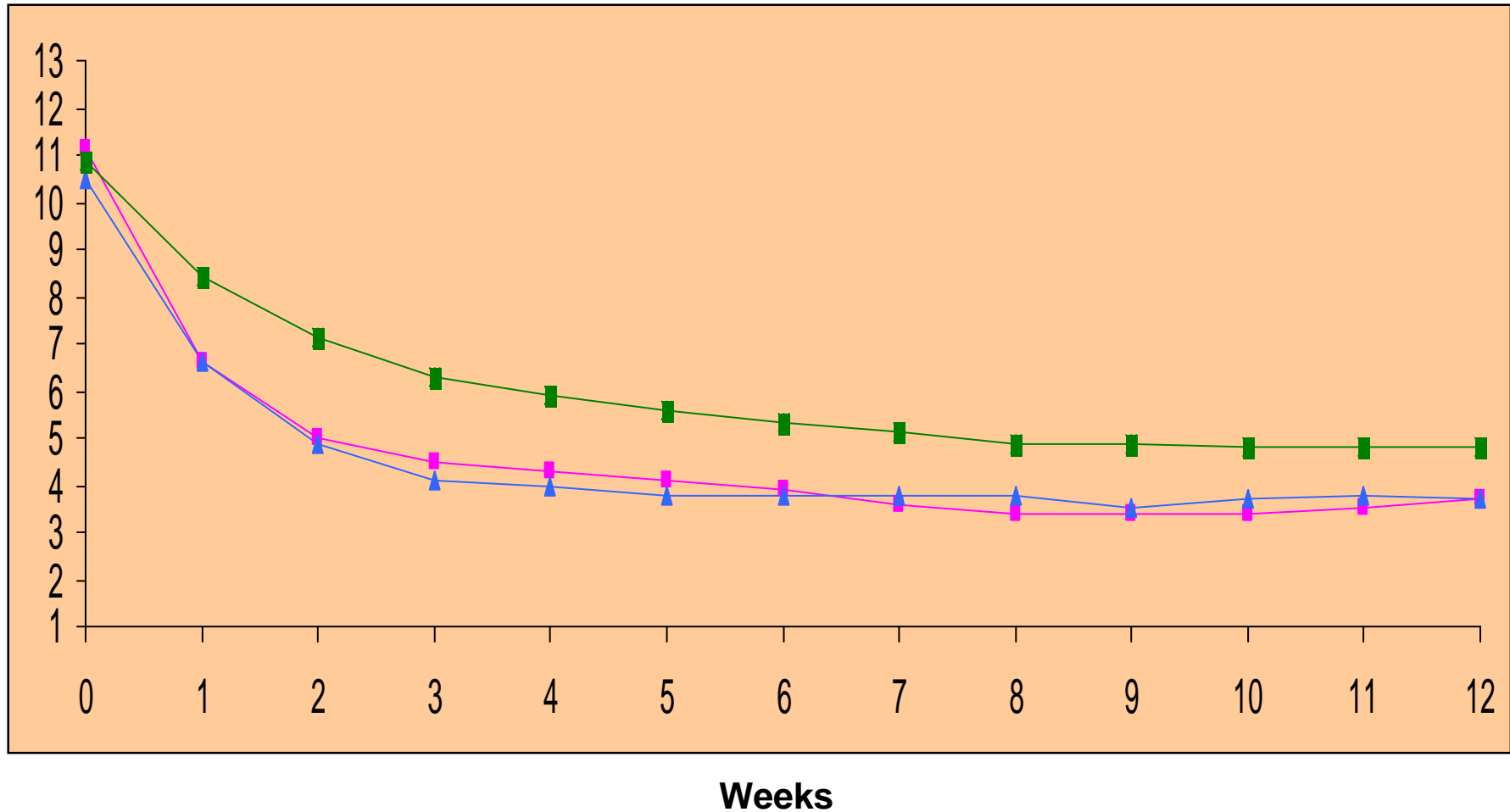
- **DVS SR**
 - Succinate salt of desvenlafaxine, major active metabolite of venlafaxine
 - Serotonin and Norepinephrine Reuptake Inhibitor
 - Unrelated to tricyclic and tetracyclic antidepressants
 - No MAO inhibition, no activity for cholinergic, H1-histaminergic or α 1-adrenergic receptors
- **Developed as non-hormonal treatment for VMS**
 - Unmet medical need
 - Some menopausal associations have included SSRI/SNRI in treatment guidelines
- **Mechanism of action/hypothesis**
 - SNRIs may relieve vasomotor instability by maintaining optimum NE/5HT balance centrally

DVS SR VMS 337– Study Design

- **Randomized controlled study**
 - **Placebo-controlled**
 - **Symptomatic postmenopausal women**
 - **Confirmed menopausal status**
 - **50 moderate to severe hot flushes per week at baseline**
 - **All had intact uterus**
- **Dosage and administration**
 - **DVS SR once daily**
 - **Titration of Desvenlafaxine**
 - **100 mg: 50 mg for 3 days, then 100 mg**
 - **150 mg: 50 mg for 3 days, followed by 100 mg for 4 days, then 150 mg**
 - **Tapering after completion of trial**
 - **100 mg: one week 50 then stop**
 - **150 mg: one week 100 mg, one week 50, then stop**

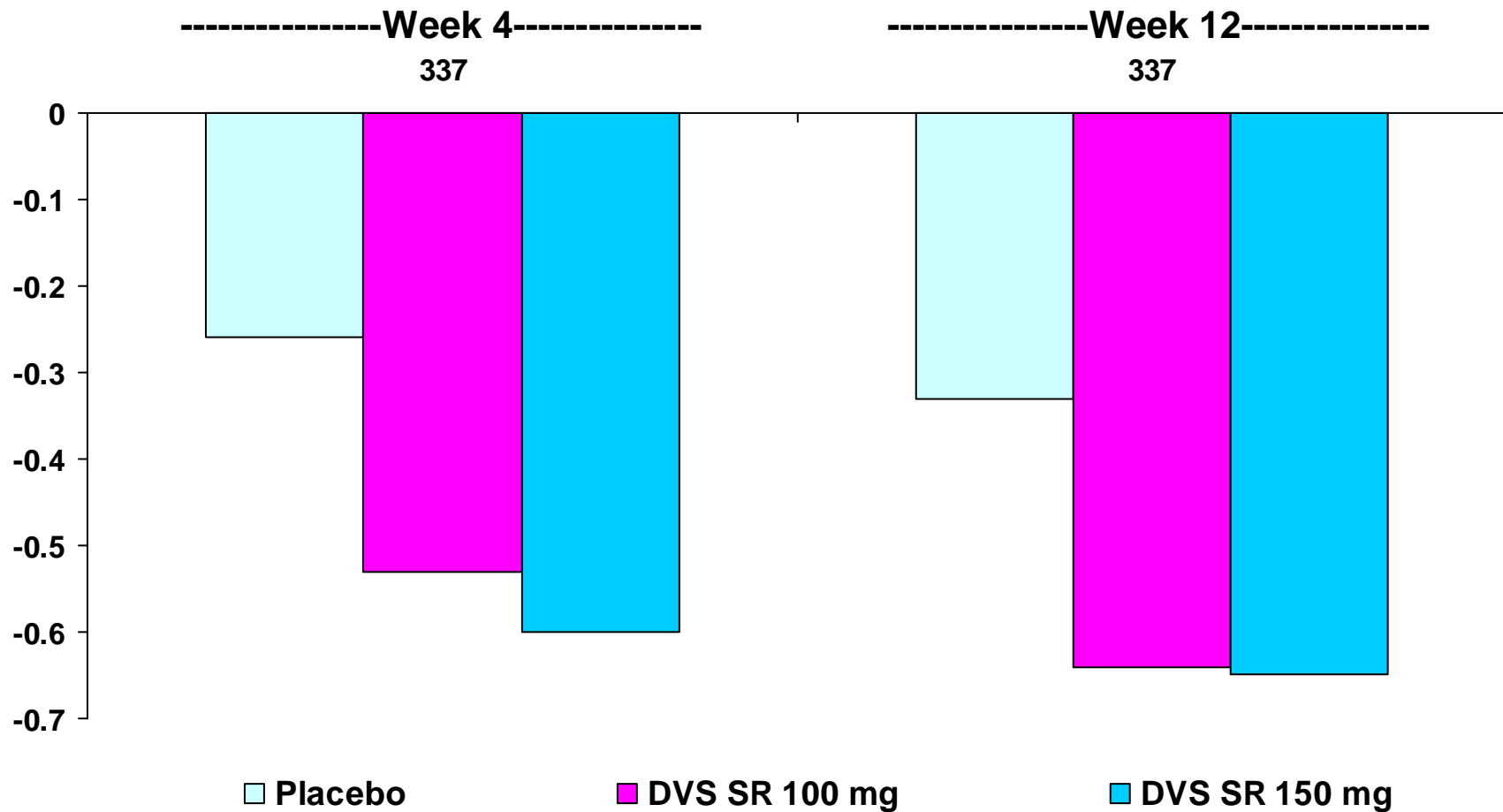
Daily Number of Moderate to Severe HF, ITT LOCF

Study 337



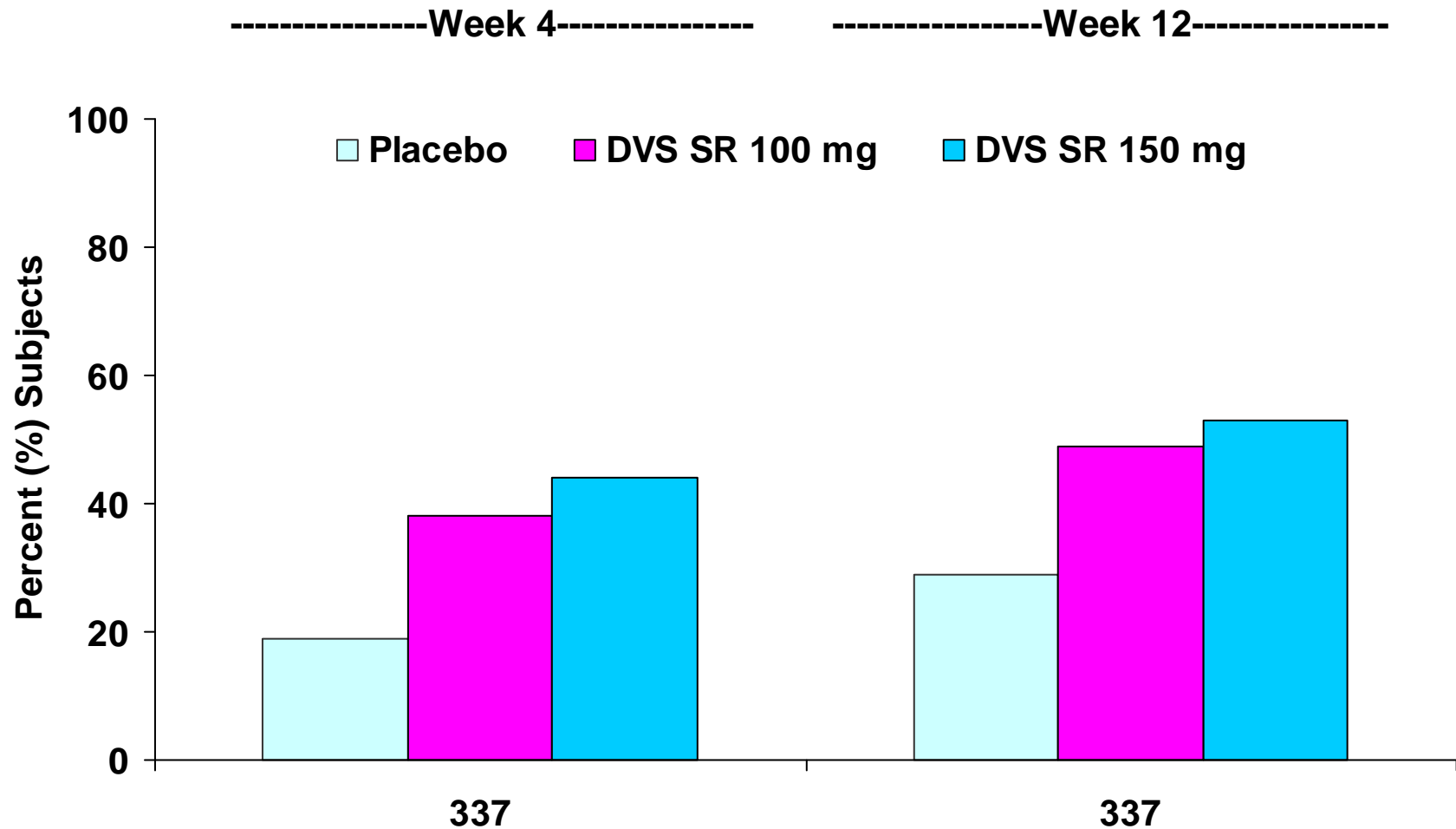
Archer DF, Abstract, ACOG 2007, San Diego, CA

Change From Baseline in Daily Severity Score, ITT LOCF



Archer DF, Abstract, ACOG 2007, San Diego, CA

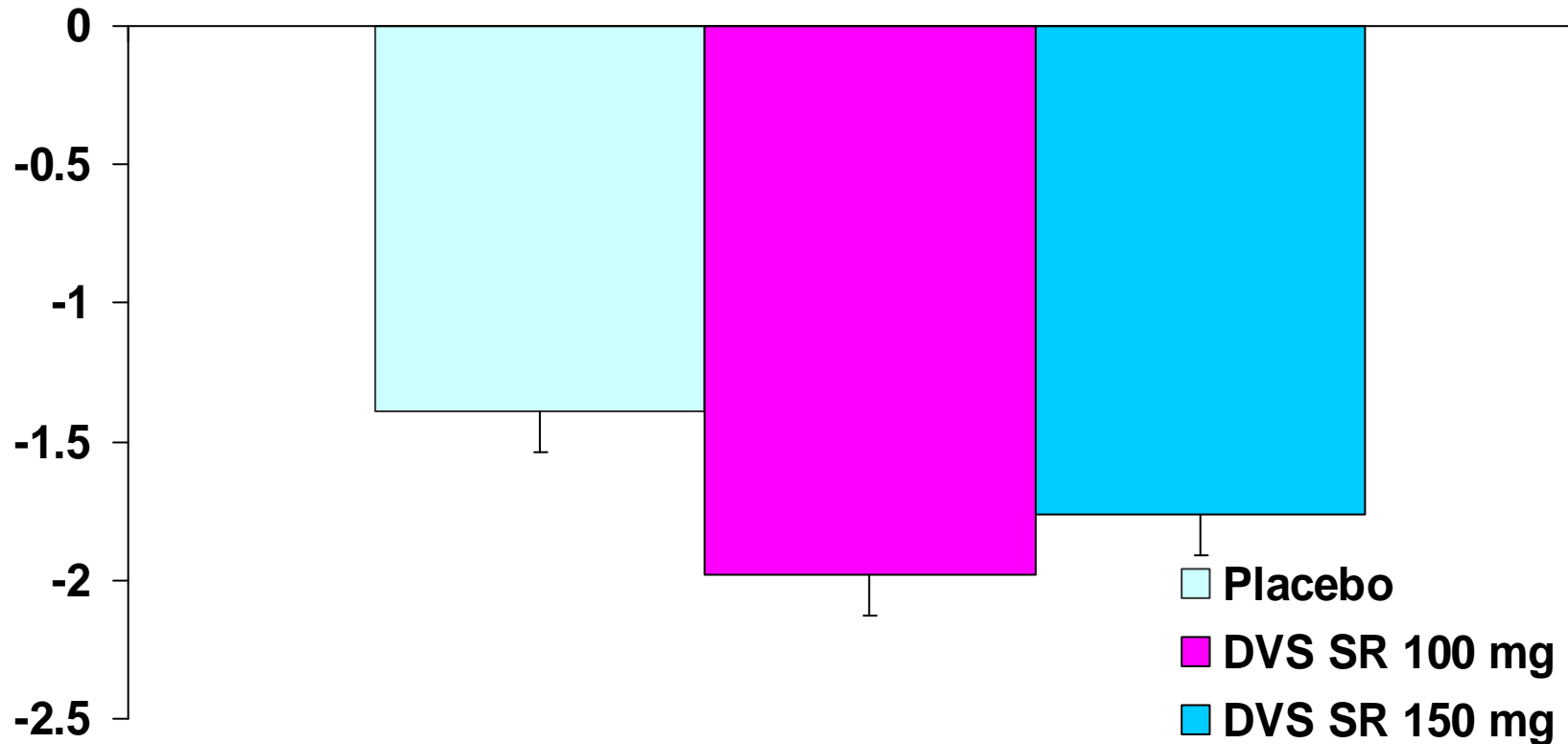
75% Responder Rate, ITT LOCF



Archer DF, Abstract, ACOG 2007, San Diego, CA

Change From Baseline in Number of Awakenings Due to HF at Week 12, ITT LOCF

Study 337



Archer DF, Abstract, ACOG 2007, San Diego, CA

Mood (POMS): Adjusted Mean Change From Baseline at Week 12, MITT LOCF

	Placebo	DVS SR 100 mg	DVS SR 150 mg
Hostility P-Value	-2.74	-5.01 <0.001	-3.93 <0.001
Confusion P-Value	-0.98	-2.37 <0.001	-1.58 0.116
Depression P-Value	-2.21	-5.42 <0.001	-4.49 0.941
Fatigue P-Value	-3.20	-4.08 0.185	-3.25 0.465
Anxiety P-Value	-2.33	-4.10 0.003	-3.83 0.011
Total Mood Score P-Value	-11.94	-22.78 <0.001	-18.01 0.045
Vigor/Activity P-Value	+0.57	+1.61 0.146	+1.01 0.540

Pairwise comparison versus placebo

Archer DF, Abstract, ACOG 2007, San Diego, CA

Nonhormonal Prescription Therapies: Clonidine

- Randomized, double-blind, placebo-controlled clinical trial¹
 - 0.1 mg/d oral
 - 194 breast cancer patients taking tamoxifen
 - Randomized, placebo-controlled
 - Hot flush frequency decreased by 38% after 8 weeks vs 24% with placebo
 - Side effects: dry mouth, drowsiness, constipation, and dizziness²

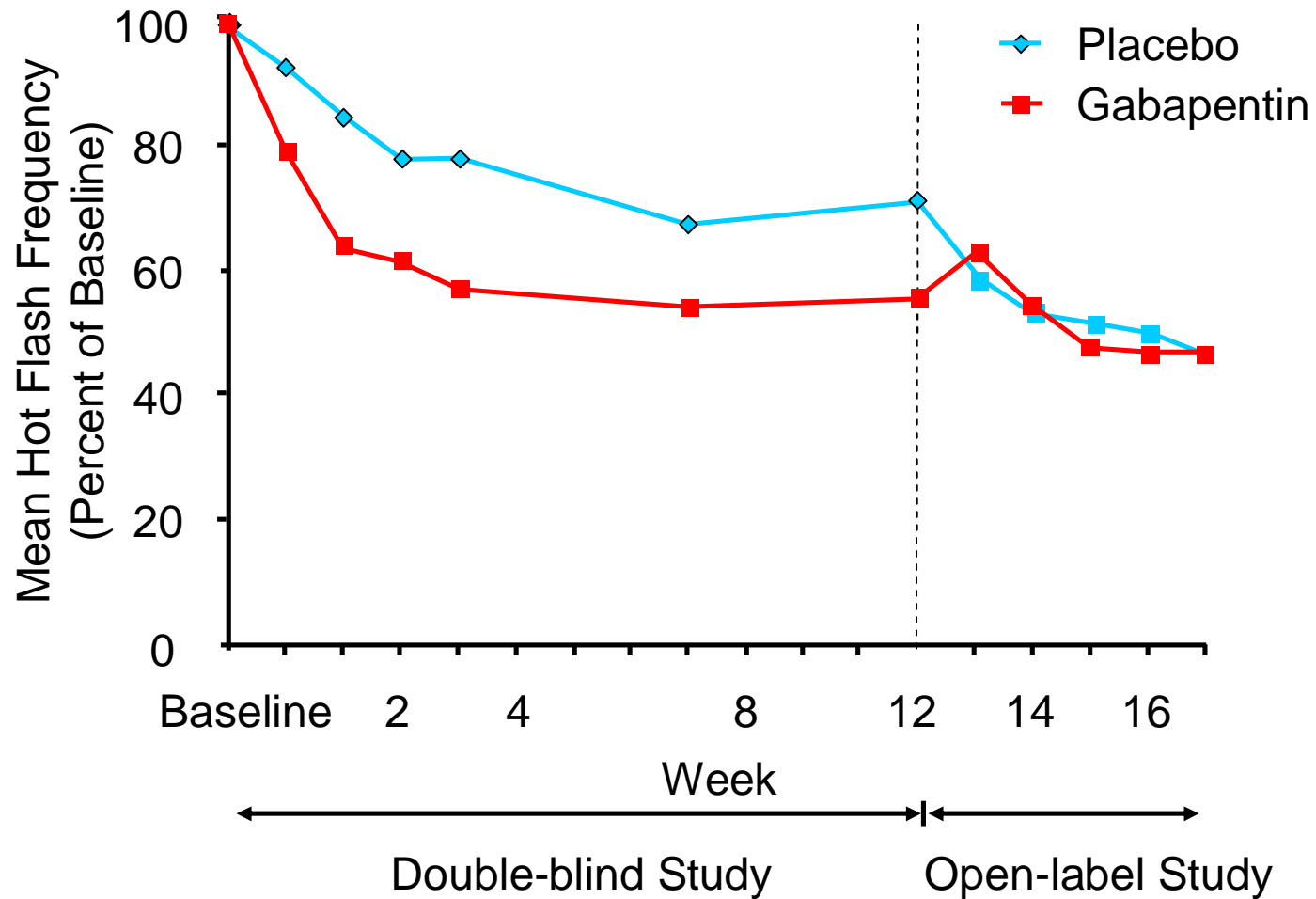
¹Pandya KJ, et al. *Ann Intern Med.* 2000;132:788-93.

²Goldberg RM, et al. *J Clin Oncol.* 1994;12:155-8.

Nonhormonal Prescription Therapies: Gabapentin

- 12-week, double-blind study**
 - Dose = 900 mg/d**
 - 7 hot flushes per day at baseline**
 - 6-week screening**
- Hot flush composite score decreased 54% vs 31% for placebo ($P = .01$)**
- 50% reported at least 1 adverse event (eg, dizziness, lightheadedness, palpitations, rash, somnolence) vs 27.6% in placebo group; 13.3% withdrew**

Gabapentin Decreases Hot Flash Frequency



Clinical Management of Vasomotor Symptoms

- **For moderate to severe vasomotor symptoms**
 - **Systemic HT remains therapeutic standard and only FDA-approved treatment for moderate to severe symptoms**
 - **Progestins effective; however, large doses required**
- **Early studies suggest limited efficacy with some SSRIs, SNRIs, and gabapentin; side effects of concern, more studies needed**
- **Desvenlafaxine results in significant improvement in hot flushes, mood, and sleep**