

Managing Menopausal Symptoms

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Disclosures

- **No ties, financial or otherwise, to pharmaceutical companies**
- **Will identify non-FDA approved treatments**

Menopause: objectives

- **Understand the epidemiology, physiology and health issues associated with menopause**
- **Diagnose and treat symptoms of menopause**
- **Integrate issues of menopause-related morbidity with symptoms**
- **Select appropriate therapies given individual symptom profile and risk factors**

MENOPAUSE:

Epidemiology

- **Cessation of menses for one year**
- **Average age in U.S: 50-51**
- **Age of menopause has not changed significantly over past 2000 years**
- **Most women spend a significant part of their lives in post-reproductive state**

Menopause: No longer a binary concept

- **Early perimenopause**
 - Significant variation in cycle length
- **Late perimenopause**
 - >60 day cycles
- **Menopause**
- **Early postmenopause**
 - The first five years after menopause
- **Late postmenopause**
 - Everything after that

Menopause: No longer a binary concept

- **Menopausal (and perimenopausal) symptoms characterize each phase of the menopausal transition**
- **Risk factors and morbidity vary widely across the menopausal transition**
- **Therefore and understanding of this continuum is critical when treating menopausal symptoms**

Menopause: Preventive Health Concerns

- **Osteoporosis**
- **Coronary artery/vascular disease**
- **Cancer (Breast, Colon, Ovary)**
- **Cognition (Alzheimer's and others)**

Menopause: Preventive Health Concerns

- **The risk of each of these disease entities increases with age**
- **Importantly, menopausal complaints do not**
- **Therefore, the role of the clinician is to integrate risk with symptoms and create individualized treatment plan**
- **Re-evaluate on a yearly basis (at least!)**

Early perimenopause symptoms

- **Early perimenopause is characterized by menstrual disturbances**
- **Longer or shorter cycles (or both!)**
- **Heavier or lighter periods (or both!)**
- **Each patient's journey is different but the destination is the same**
 - **Kind of like puberty**
- **Contraception!!! (also kind of like puberty)**

Late perimenopause symptoms

- **Increasing degree of estrogen deficiency**
 - **More vasomotor issues**
 - **Increasing sexual dysfunction**
 - **Urogenital atrophy**
 - **Multiple other**
- **Still the occasional menstrual period**
 - **High incidence of HRT-related bleeding**

Early menopause symptoms

- **Similar to late perimenopause – without the periods**
- **Peak hot-flash time!**

- **Late menopause**
 - **urogenital atrophy ongoing**
 - **Fewer/more manageable hot flashes**

Menopause

Lifestyle changes for all age groups

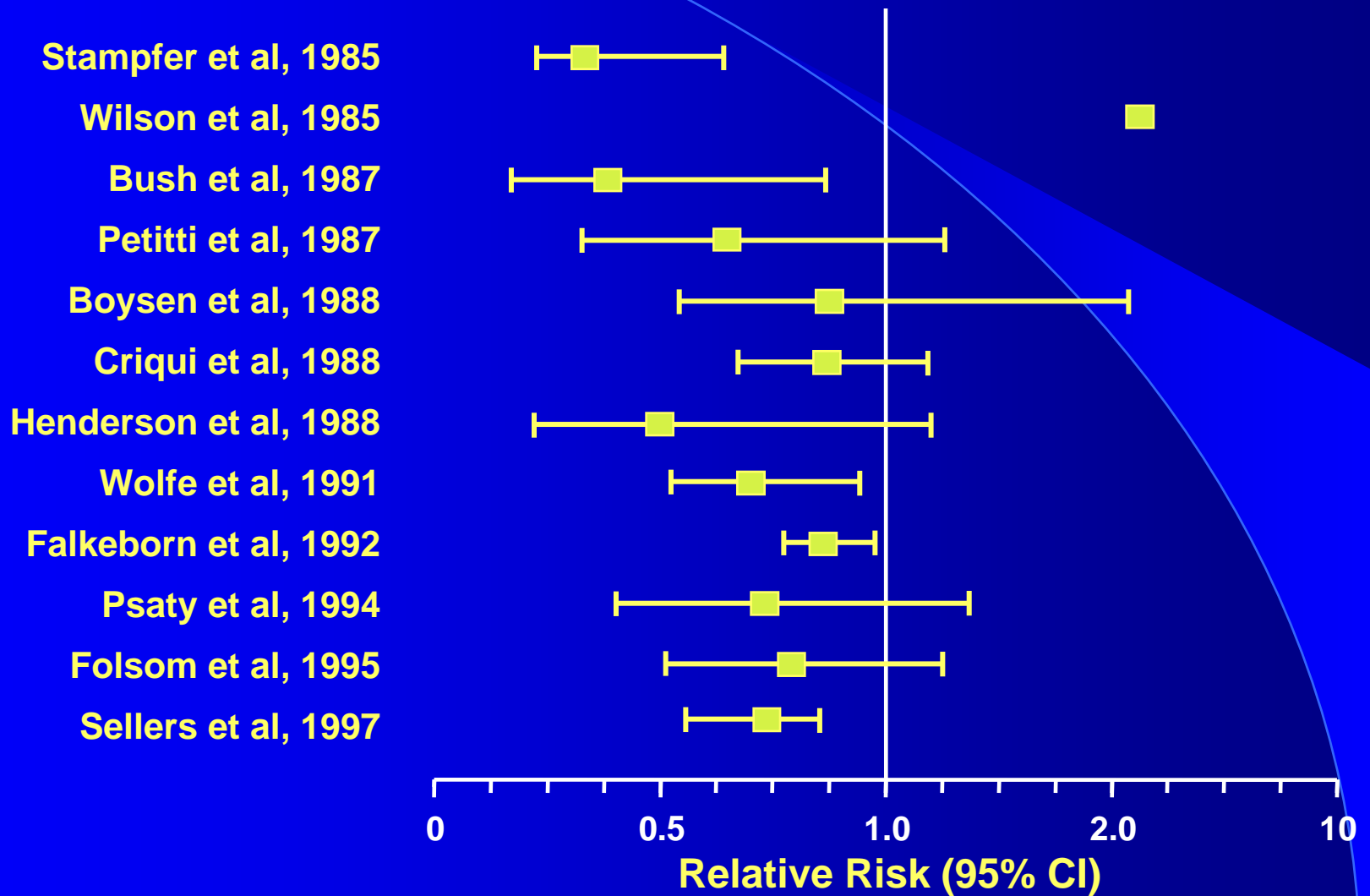
- Stop smoking
- Lose weight
- Exercise
- Decrease fat intake

Treatment of menopausal symptoms: HRT

Menopause and HRT: A tour through history, with the usual pendulum swings

- **ERT originally marketed/prescribed for relief of postmenopausal symptoms (1960's, 70's)**
- **These symptoms included hot flashes, mood swings, insomnia – i.e. quality of life issues**
- **Over time it became apparent that women who chose HRT derived important health benefits**
 - **Protection from osteoporosis and heart disease**

Observational Studies of CVD Risk and ERT/HRT



Benefits of HRT

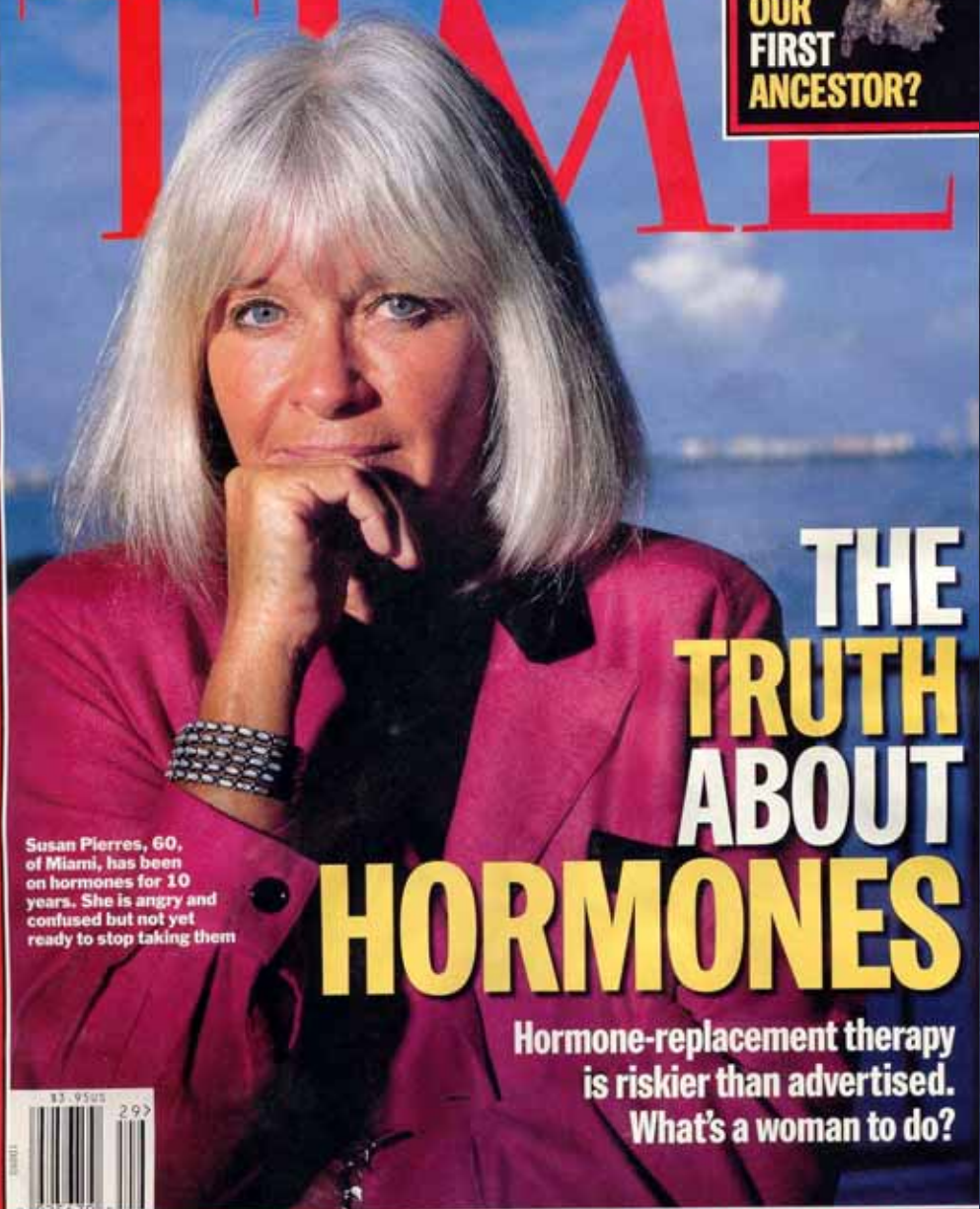
- **However, important criticisms of studies finding health benefits to HRT**
 - **Many studies were not randomized**
 - **Those that were, often measured “surrogate markers” for heart disease: Cholesterol levels, not actual heart attacks**

JULY 22, 2002

WALL STREET: LOSING SAVINGS—AND TRUST

TIME

IS THIS OUR FIRST ANCESTOR?



Susan Pierres, 60, of Miami, has been on hormones for 10 years. She is angry and confused but not yet ready to stop taking them

THE TRUTH ABOUT HORMONES

Hormone-replacement therapy is riskier than advertised. What's a woman to do?



www.time.com AOL Keyword: TIME

INSIDE HARKEN AND HALLIBURTON • THE OLDEST SKULL

Newsweek

July 22, 2002

newsweek.abc.com



A New Study Raises Fears About the Risks For Millions Of Women. Here's What You Should Do

Beyond Hormone Therapy



WHI Results

Absolute and Relative Risk or Benefit of CEE/MPA

<i>Health Event</i>	<i>Overall Hazard Ratio</i>	<i>95% CI</i>	<i>Increased Absolute Risk per 10,000 Women/Year</i>	<i>Increased Absolute Benefit per 10,000 Women/Year</i>
CHD	1.29	1.02–1.63	7	
Strokes	1.41	1.07–1.85	8	
Breast cancer	1.26	1.00–1.59	8	
VTED	2.11	1.58–2.82	18	
Colorectal cancer	0.63	0.43–0.92		6
Hip fractures	0.66	0.45–0.98		5
Total fractures	0.76	0.69–0.85		44

CHD = coronary heart disease; VTED = venous thromboembolic disease.

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-33.

WHI Results

Absolute and Relative Risk or Benefit of CEE only

<i>Health Event</i>	<i>Overall Hazard Ratio</i>	<i>95% CI</i>	<i>Increased Absolute Risk per 10,000 Women/Year</i>	<i>Increased Absolute Benefit per 10,000 Women/Year</i>
CHD	0.91	0.75-1.12		5
Strokes	1.39	1.10-1.77	12	
Breast cancer	0.77	0.59-1.01		7
Colorectal cancer	1.08	0.75-1.55	1	
Hip fractures	0.61	0.41-0.91		6
Total fractures	0.70	0.63-0.79		56

CHD = coronary heart disease

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2004;291:1701-12.

**WHI (and all the other randomized data) vs. Nurses'
Health Study
(and all the other observational data):**

Why the difference???

WHI vs. NHS: Why the difference?

Baseline characteristics

	<i>WHI</i>	<i>NHS</i>
Mean age or age range at enrollment (years)	63	30-55
Smokers	49.9%	6.9%
Body mass index (BMI; mean)	28.5 kg/m ² *	25.1 kg/m ²
Aspirin users	19.1%	43.9%

*34.1% had BMI ≥ 30 kg/m².

Grodstein F et al. *Ann Intern Med.* 2000;133:933-41.

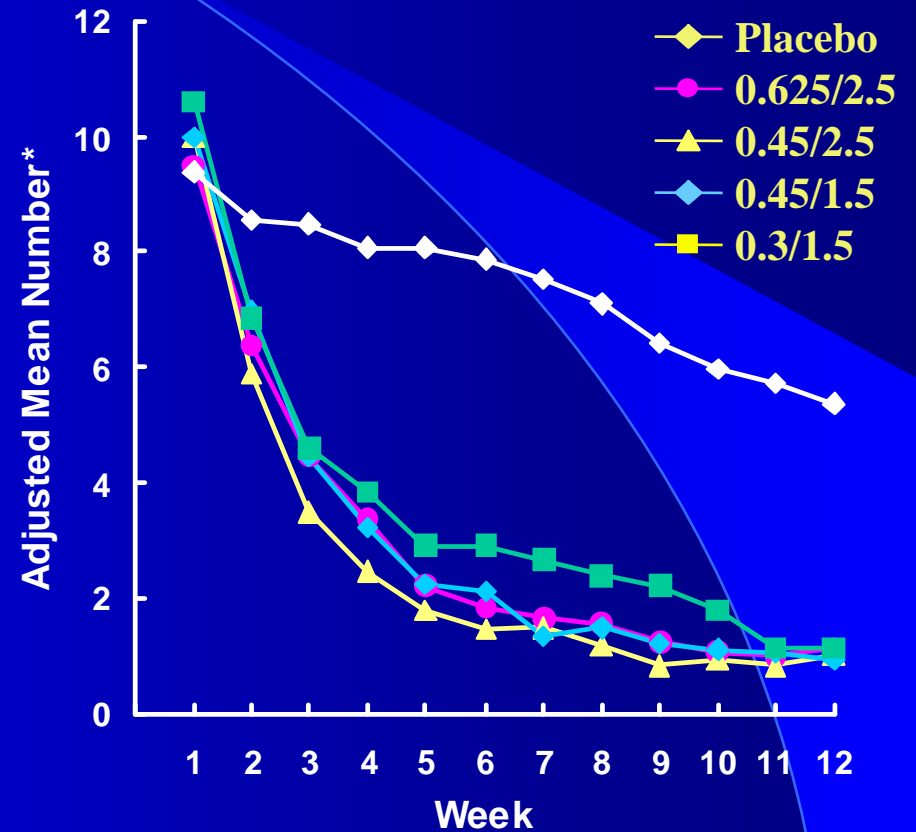
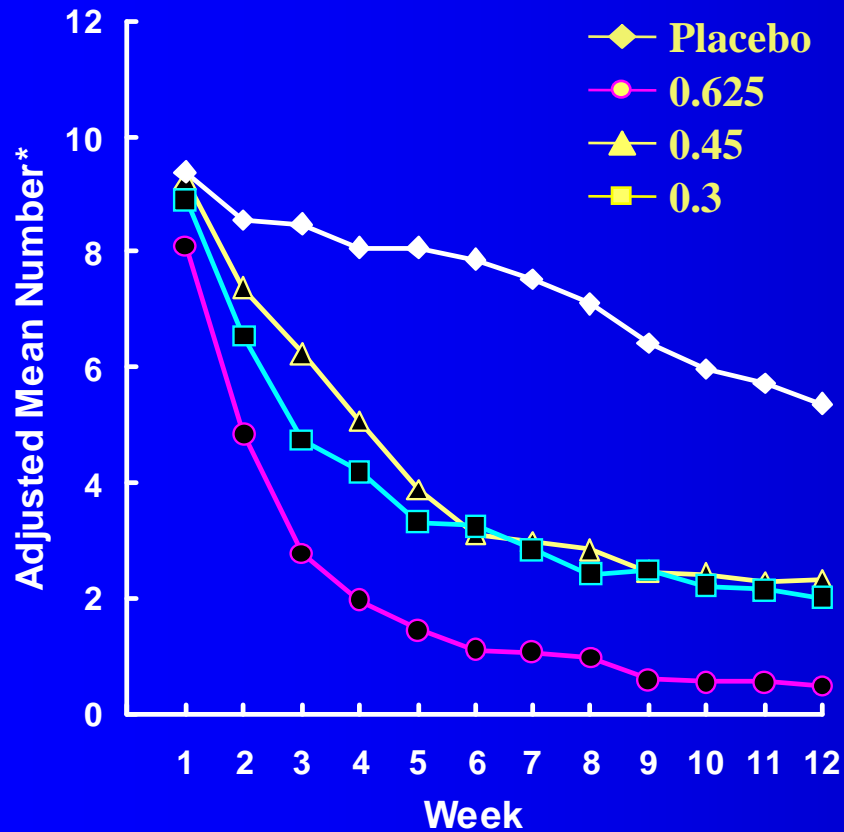
Grodstein F et al. *N Engl J Med.* 1996;335:453-61.

Writing Group for the Women's Health Initiative Investigators. *JAMA.* 2002;288:321-33.

HRT after the WHI

- **The search is on for alternative ways to treat menopausal symptoms**
 - **Lower doses of previously studied hormonal preparations**
 - **New delivery systems**
 - **Non-hormonal drugs**

Estrogen for vasomotor symptoms with/without progestin



*Adjusted for baseline.
 Mean hot flashes at baseline = 12.3 (range 11.3–13.8).

Available preparations (FDA approved) for menopausal symptoms

- 43 preparations to date
- More coming all the time
- <http://www.empr.com/menopause-and-hrt/category/113/0/>
- DH formularies carry many HRT formulations

Estrogen-based therapy for vasomotor symptoms

Contents	Dose	Route	Frequency
Conjugated equine estrogens	0.3-1.25 mg	Oral	Daily
Synthetic conjugated estrogens	0.3-1.25 mg	Oral	Daily
Estradiol	0.5-1 mg	Oral	Daily
Esterified Estrogens	0.3-2.5 mg	Oral	Daily
Estropipate	0.75-1.5 mg	Oral	Daily
Estradiol Acetate	0.45-1.8 mg	Oral	Daily

Non-oral delivery systems for estrogen

Contents	Dose	Route	Frequency
Estradiol	0.014-0.1 mg	Patch	1-2x/week
Estradiol	0.25-3 mg	Gel	Daily
Estradiol	1.53 mg	Spray	Daily

Alternative treatment for hot flushes

- **Clonidine: 0.1 mg patch**
 - **Historically, one of the few non-hormonal treatments available for patients with contraindication to ERT**
 - **Mixed results, side effects (hypotension)**

Alternative treatment for hot flushes

- **Gabapentin (Neurontin)**
 - RCT of gabapentin vs. placebo
 - 24 women with severe HF
 - Dose: 300-900 mg/day for 4 weeks
 - 70% decrease in HF severity score

- Loprinzi CL. *Mayo Clin Proc* 2002;77:1159-1163

Alternative treatments for hot flushes

- **Fluoxetine (Prozac)**
 - 81 women, 4-week placebo crossover trial*
 - Dose: 20 mg/day
 - 50% reduction in HF (36% placebo)
 - Also studied: venlafaxine (Effexor) 37.5 mg/day and other SSRIs – superior to placebo
 - *Loprinzi CL. *J Clin Oncol* 2002(March); 20:1578-1583

Alternative treatments for hot flushes

- **Soy**
 - **Placebo-controlled, 16-week trial**
 - **Dose: 70 mg/day soy isoflavone extract**
 - **61.2% HF reduction (20.8% placebo)**
 - **Note: concentrated extract of soy – need large amt. of soy-based food to equal this**
 - **Faure ED. *Menopause* 2002;9:329-334**

Phytoestrogens

- **Some phytoestrogens, taken in pharmacologic doses, may help with symptomatic control of hot flashes**
- **Quantities needed to protect bone, reverse urogenital atrophy etc. are likely much higher than those studied for hot flashes**
- **Soy may be contraindicated in women with breast cancer**

Complementary Medicine

- **Many herbal preparations claim to ameliorate menopausal symptoms**
- **Herbs are drugs! If taken in doses high enough to achieve symptom relief, it follows that they may also carry similar risks to conventional HRT**

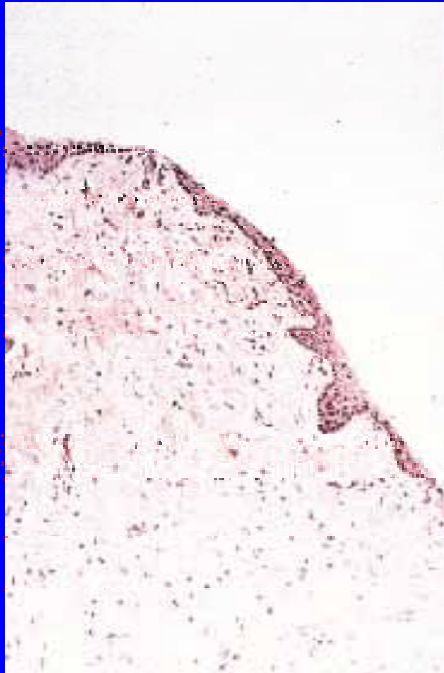
FDA-approved, non-HRT alternatives for osteoporosis treatment/prevention

- **Bisphosphates**
 - **Alendronate (Fosamax) 70 mg/week**
 - **Risedronate (Actonel) 35 mg/week**
- **SERMs**
 - **Raloxifene (Evista) 60 mg/day**
 - **Others in development**
- **Calcitonin (Miacalcin) nasal spray**

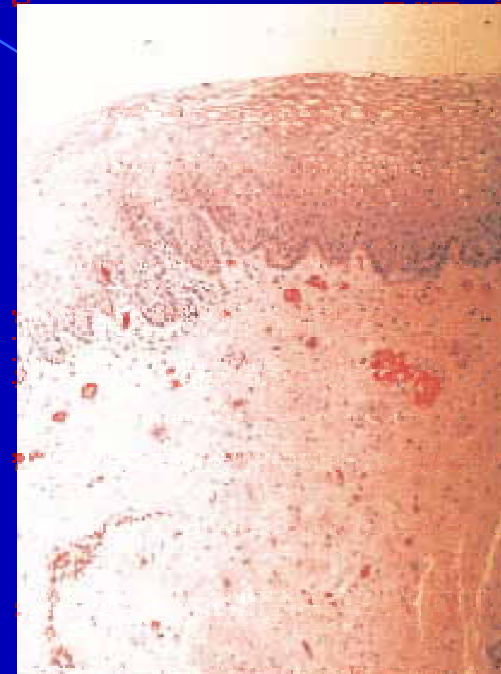
Vaginal/urological Symptoms Associated With Estrogen Deficiency

- Irritation
- Burning
- Pruritis
- Leukorrhea, vaginal discharge
- Dyspareunia
- Decreased vaginal secretions
- Shortening/lessening of vaginal distensibility
- Incontinence
- UTI's

Vaginal Epithelium and ERT



6 weeks of
estrogen



Without estrogen – atrophic

With estrogen

- Vagina/urethra highest concentration of estrogen receptors
- Most efficient response with local application, however systemic therapy also effective

Alternatives to systemic ERT for urogenital atrophy

- **OTC lubricants**
- **Estring – minimal systemic absorption**
- **Estrogen vaginal tablets – minimal**
- **Estrogen cream – higher absorption; exact pharmacokinetics are the subject of ongoing study**

And now, a word (or two): “bioidentical” hormones

- **Definition: “Bioidentical” means any compound that is normally found in the human body**
- **Practically speaking, “bioidentical hormone therapy” has come to refer to use of various hormonal preparations, compounded by a pharmacist and individualized to treat symptoms of menopause**
- **Initial workup and testing (“hormone levels”)**
- **Workup and ongoing treatment not covered by insurance**
- **\$1000 initially, \$30-75/month maintenance**





COURTESY: HARPO INC.

Bioidentical HRT: Issues

- **The chief criticism of “bioidentical” HRT is not that it does not work (it certainly might)**
 - **Not as rigorously studied for safety implications**
 - **No evidence that serum hormone levels can inform accurate dosing**
 - **Companies claim superior results to conventional HRT, with inadequate evidence**

Bioidenticals: FDA position

- **FDA Seeks Enforcement of So-Called “Bioidentical” Compounds**

In early January, the U.S. Food and Drug Administration (FDA) announced that it had sent letters warning seven pharmacy operations that the claims they make about the safety and effectiveness of their so-called "bioidentical hormone replacement therapy," or "BHRT" products are **unsupported by medical evidence**, and are **considered false and misleading** by the agency. FDA is concerned that unfounded claims like these mislead women and health care professionals.

The pharmacy operations **improperly claim that their drugs**, which contain hormones such as estrogen, progesterone, and estriol (which is not a component of an FDA approved drug and has not been proven safe and effective for any use) **are superior** to FDA-approved menopausal hormone therapy drugs **and prevent or treat serious diseases**, including Alzheimer's disease, stroke, and various forms of cancer.

FDA is concerned that the claims for safety, effectiveness, and superiority that these pharmacy operations tout are misleading patients, as well as doctors and other health care professionals. **Compounded drugs are not reviewed by the FDA** for safety and effectiveness, and FDA encourages patients to use FDA-approved drugs whenever possible. The warning letters state that the pharmacy operations violate federal law by making false and misleading claims about their hormone therapy drugs.

And if that is not confusing enough...

- **Is your patient androgen “deficient”?**
 - **Low sex drive**
 - **Change in body fat distribution**
 - **Depressed mood**
 - **Fatigue**
- **If so should she be taking testosterone? Viagra?**



- What, exactly, is “mojo”?
- Are you randy, baby?

Testosterone supplementation

- Oral testosterone absorption is significantly impaired by first-pass hepatic effect
- Androgen patches are FDA approved for men
 - 2.4 mg/day
- Androgen patches have been investigated for women
 - 150-300 mcg/day

Physiology of testosterone

- **Normal testosterone levels (women)**
 - **0.2 – 0.3 mg/day produced**
 - **Serum 20-80 ng/dl in reproductive women**
 - **Increases 10-20% mid cycle**
 - **Fall by 40-60% at natural menopause**
 - **Fall by similar amounts with OCP use**
 - **Fall by 80% with surgical menopause**

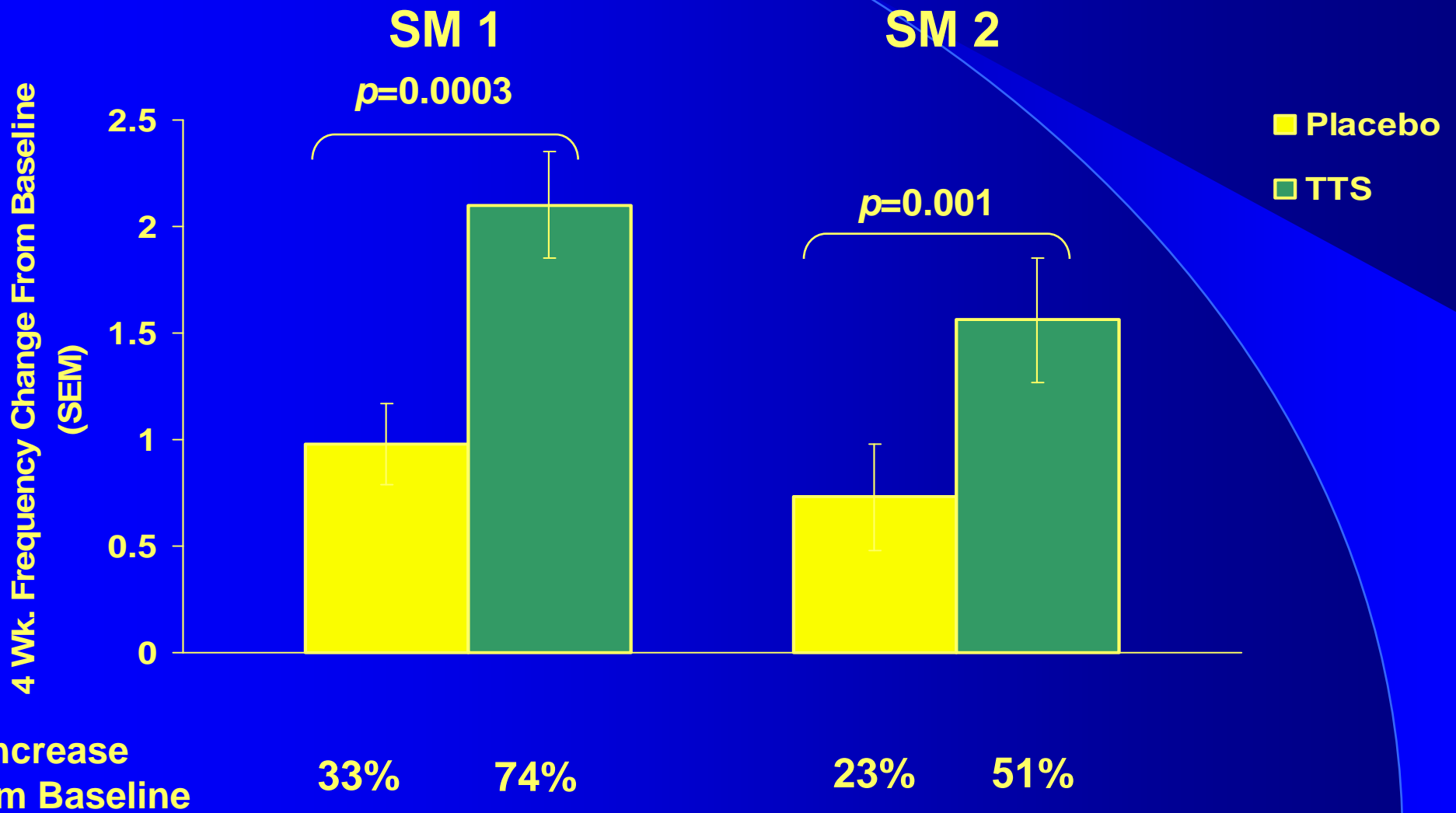
Testosterone levels in women with low libido

- Schreiner-Engel P. Horm Behav 1989;23:221
- 17 women with ISD compared to 13 normal controls
- Blood samples were drawn every 3 to 4 days for one menstrual cycle and were analyzed by RIA for testosterone, SHBG, estradiol, progesterone, prolactin, and luteinizing hormone
- No differences noted in the two groups

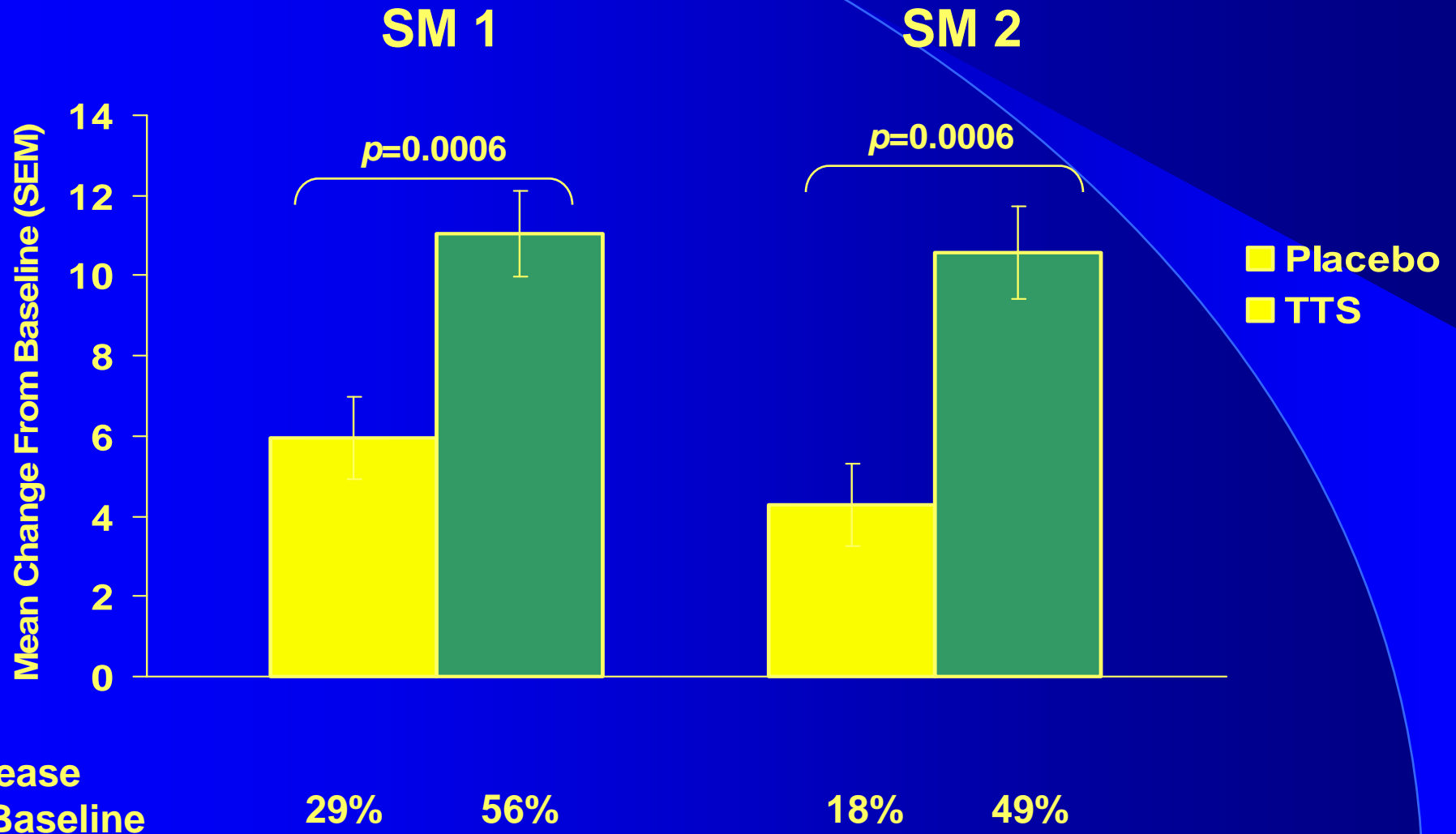
Testosterone post menopause

- **Kirchengast, Maturitas 1996;23:63-71**
- **The relationship between body build, androgen levels and changes in sexual interest after menopause was investigated in 171 postmenopausal women from Vienna, Austria**
- **Statistically significant associations between androgen levels and decrease in sexual interest could not be demonstrated**

Testosterone Patch Increased Total Satisfying Sexual Activity at 24 Weeks



Testosterone Patch Increased Desire at 24 Weeks



% Increase From Baseline

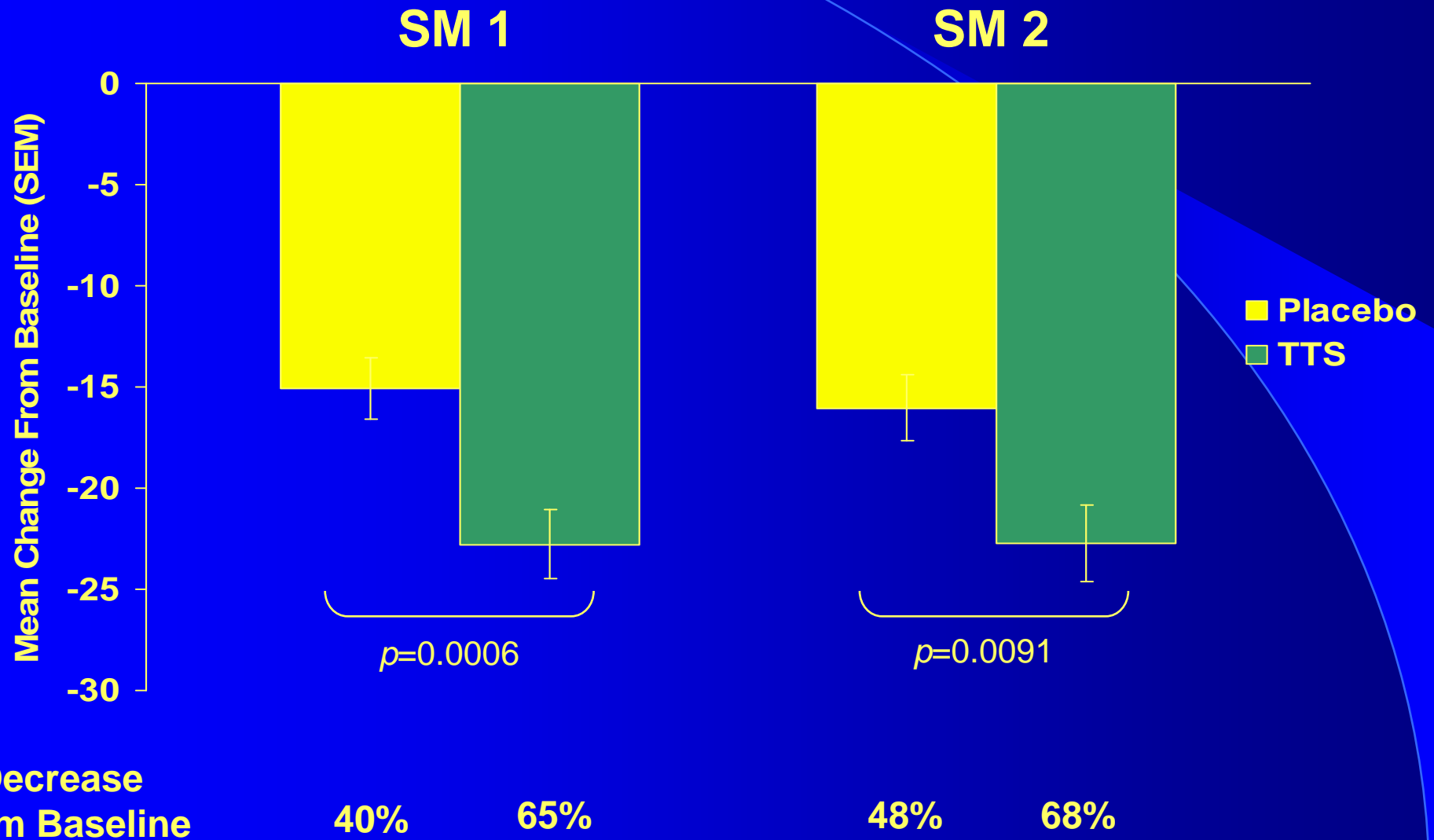
29%

56%

18%

49%

Testosterone Patch Decreased Distress at 24 Weeks



% Decrease From Baseline

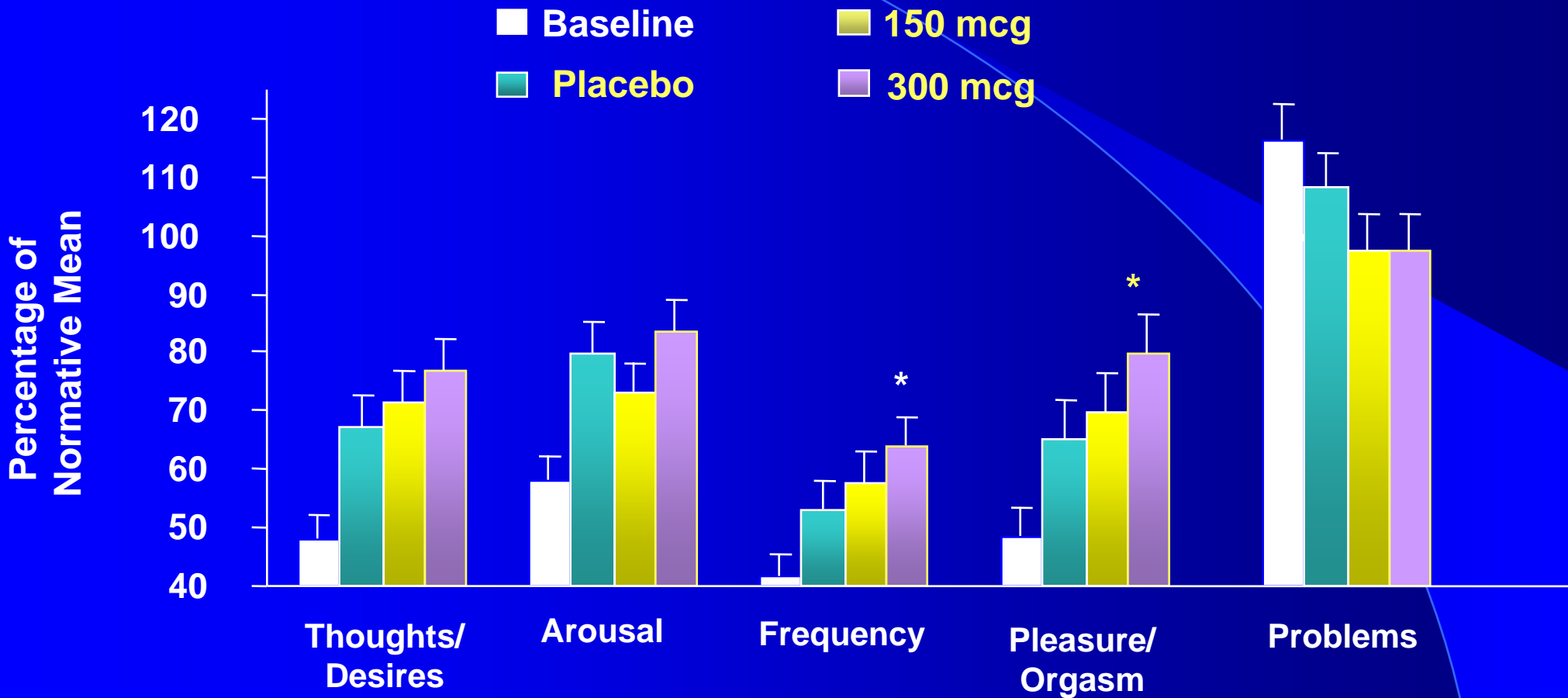
40%

65%

48%

68%

Estrogen and Testosterone Patch: Sexual Function



N=75; * $P < 0.05$ for comparison with placebo

Shifren JL, et al. *N Engl J Med.* 2000;343:682-688.

The value of T for menopausal women

- Clinical effects of T are probably real
- But, for women they represent a small fraction of the overall picture
- No study will ever be large enough to show safety to the degree demanded by the FDA and the public



Managing the menopause

- Maximize lifestyle, non-pharmacologic preventions/treatments
- There are no “correct” answers for HRT
- Estrogen is rarely absolutely contraindicated
- It is important to consider individual risks and benefits and patient preferences
- Tailor therapy to maximize benefits, and minimize risks and side effects
- Re-assess on a yearly basis – have a rationale for what you do!!

Thank you