The National Academies of SCIENCES ENGINEERING MEDICINE

CLINICAL UTILITY OF TREATING PATIENTS WITH COMPOUNDED "BIOIDENTICAL HORMONE REPLACEMENT THERAPY"

Second Committee Meeting Agenda

Monday, May 6, 2019

SESSION 1 Context for the Current Study
9:10 am. Overview Session

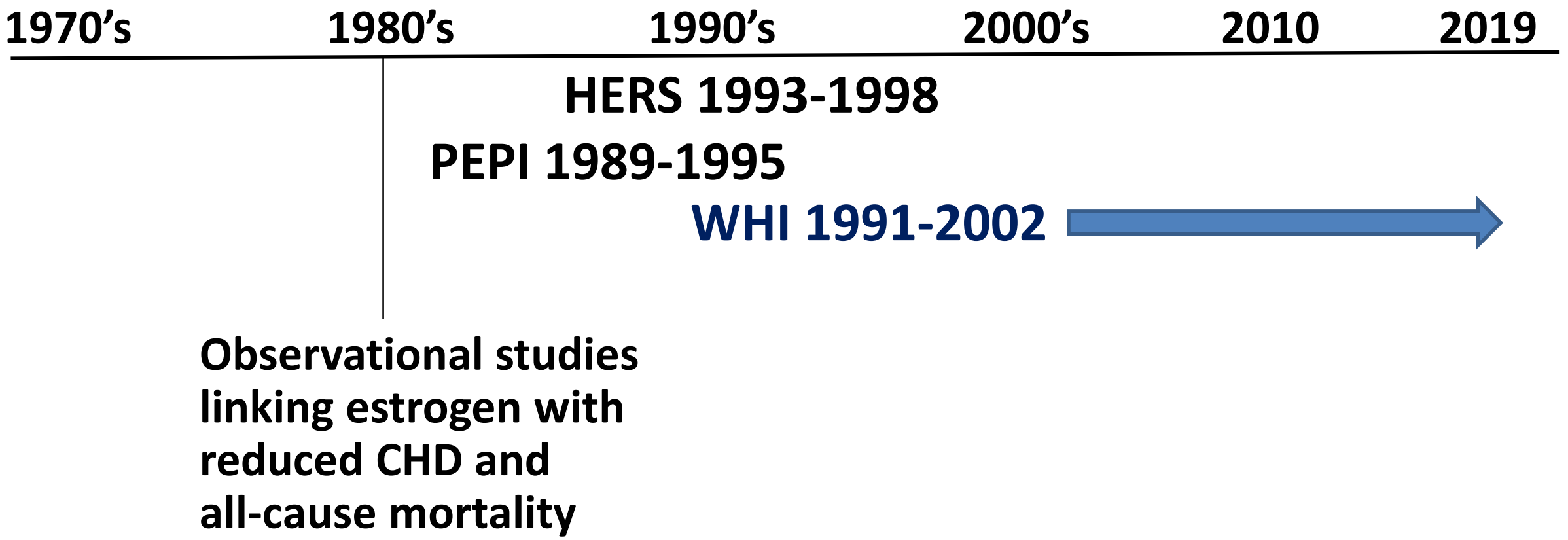
Cynthia A. Stuenkel, MD
University of California, San Diego

Emergence and Clinical Utility of cBHRT Products

Presentation Objectives:

- An historical perspective
- Major outcomes from the Women's Health Initiative trials
- Current trends in use of cBHRT
- Clinical safety and utility of cBHRT
- Comparison of safety and utility of cBHRT vs. FDA-approved hormone therapy products

History of MHT Research in Menopausal Women



CHD, coronary heart disease; PEPI, Postmenopausal Estrogen and Progestin Intervention Trial
HERS, Heart and Estrogen-Progestogen Replacement Study; WHI, Women's Health Initiative


WOMEN'S
HEALTH
INITIATIVE

WHI Intervention Phases

Intervention

- **CEE + MPA** Results 2002

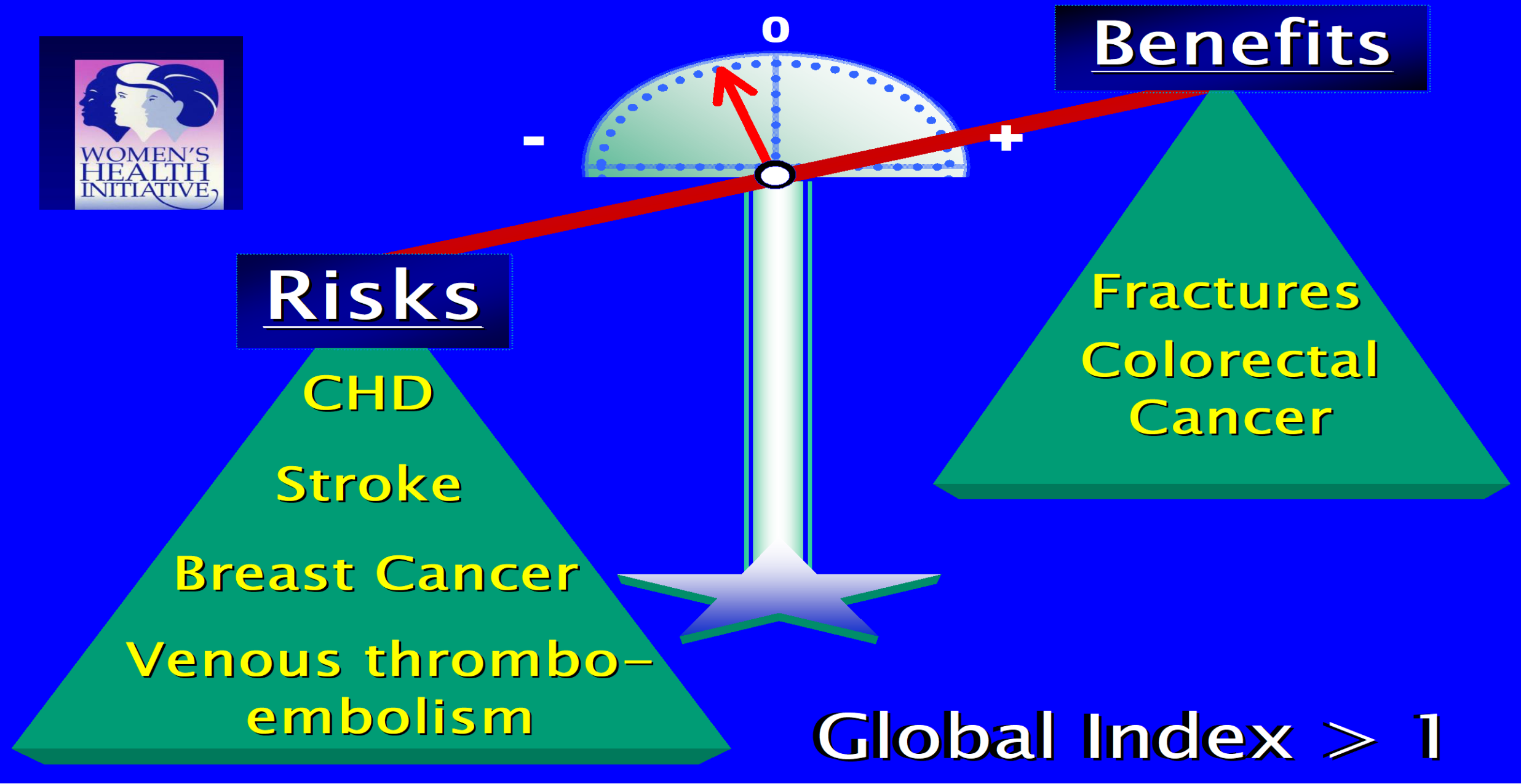
5.6 y

- **CEE-alone** Results 2004

7.2 y

CEE, conjugated equine estrogens, 0.625 mg; MPA, medroxyprogesterone acetate, 2.5 mg
Manson JE, et al. *JAMA* 2013; 310:1353; figure CA Stuenkel, 2014.

Long-Term Administration of HT



Global Index > 1

WHI: Immediate Impact

- The FDA required package labeling changes for all hormone therapy preparations within months of the 2002 publication of the combined therapy results.

FDA Labels for Estrogen and Estrogen with Progestin Therapy

MODIFIED APPROVED INDICATIONS

1. **Treatment of moderate to severe vasomotor symptoms associated with the menopause**

   - Prescribe at the lowest dose and for the shortest duration for the individual woman

FDA Labels for Estrogen and Estrogen with Progestin Therapy

MODIFIED APPROVED INDICATIONS

2. **Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (dryness and irritation) associated with the menopause**

-When prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, consider topical vaginal products

FDA Labels for Estrogen and Estrogen with Progestin Therapy

MODIFIED APPROVED INDICATIONS

3. **Prevention of postmenopausal osteoporosis**

-If hormone therapy is prescribed for osteoporosis, women should be at significant risk for osteoporosis and unable to take non-estrogen medications.

www.fda.gov 1/8/03; 2/10/04

FDA Labels for Estrogen and Estrogen with Progestin Therapy

NEW BOXED WARNING

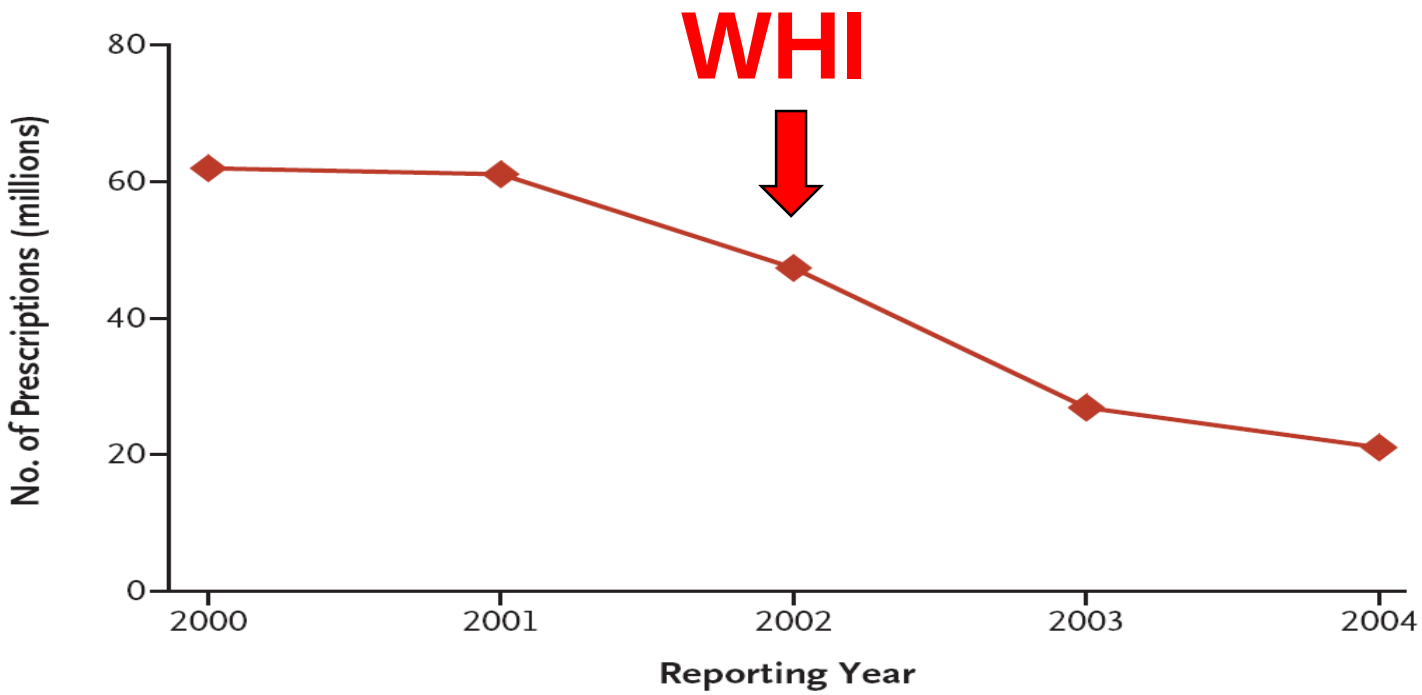
- Highlights the increased risks for heart disease, heart attacks, strokes, and breast cancer
- Emphasizes that these products are not approved for heart disease prevention
- Similar label changes requested for all other manufacturers of estrogen and estrogen with a progestin because **all products are believed to have similar risks**

www.fda.gov 1/8/03

WHI: Immediate Impact on Prescribing

- Prescriptions for combined hormone therapy (CEE and MPA) dropped precipitously.

2000-2004



Ravdin PM, et al. *N Engl J Med* 2007; 356:1670-1674.

JAMA The Journal of the American Medical Association

Research

Original Investigation

Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials

JoAnn E. Manson, MD, DrPH; Rowan T. Chlebowski, MD, PhD; Marcia L. Stefanick, PhD; Aaron K. Aragaki, MS; Jacques E. Rossouw, MD; Ross L. Prentice, PhD; Garnet Anderson, PhD; Barbara V. Howard, PhD; Cynthia A. Thomson, PhD, RD; Andrea Z. LaCroix, PhD; Jean Wactawski-Wende, PhD; Rebecca D. Jackson, MD; Marian Limacher, MD; Karen L. Margolis, MD, MPH; Sylvia Wassertheil-Smoller, PhD; Shirley A. Beresford, PhD; Jane A. Cauley, DrPH; Charles B. Eaton, MD, MS; Margery Gass, MD, NCMP; Judith Hsia, MD; Karen C. Johnson, MD, MPH; Charles Kooperberg, PhD; Lewis H. Kuller, MD, DrPH; Cora E. Lewis, MD, MSPH; Simin Liu, MD, ScD; Lisa W. Martin, MD; Judith K. Ockene, PhD; Mary Jo O'Sullivan, MD; Lynda H. Powell, PhD; Michael S. Simon, MD, MPH; Linda Van Horn, PhD, RD; Mara Z. Vitolins, DrPH, RD; Robert B. Wallace, MD, MSc

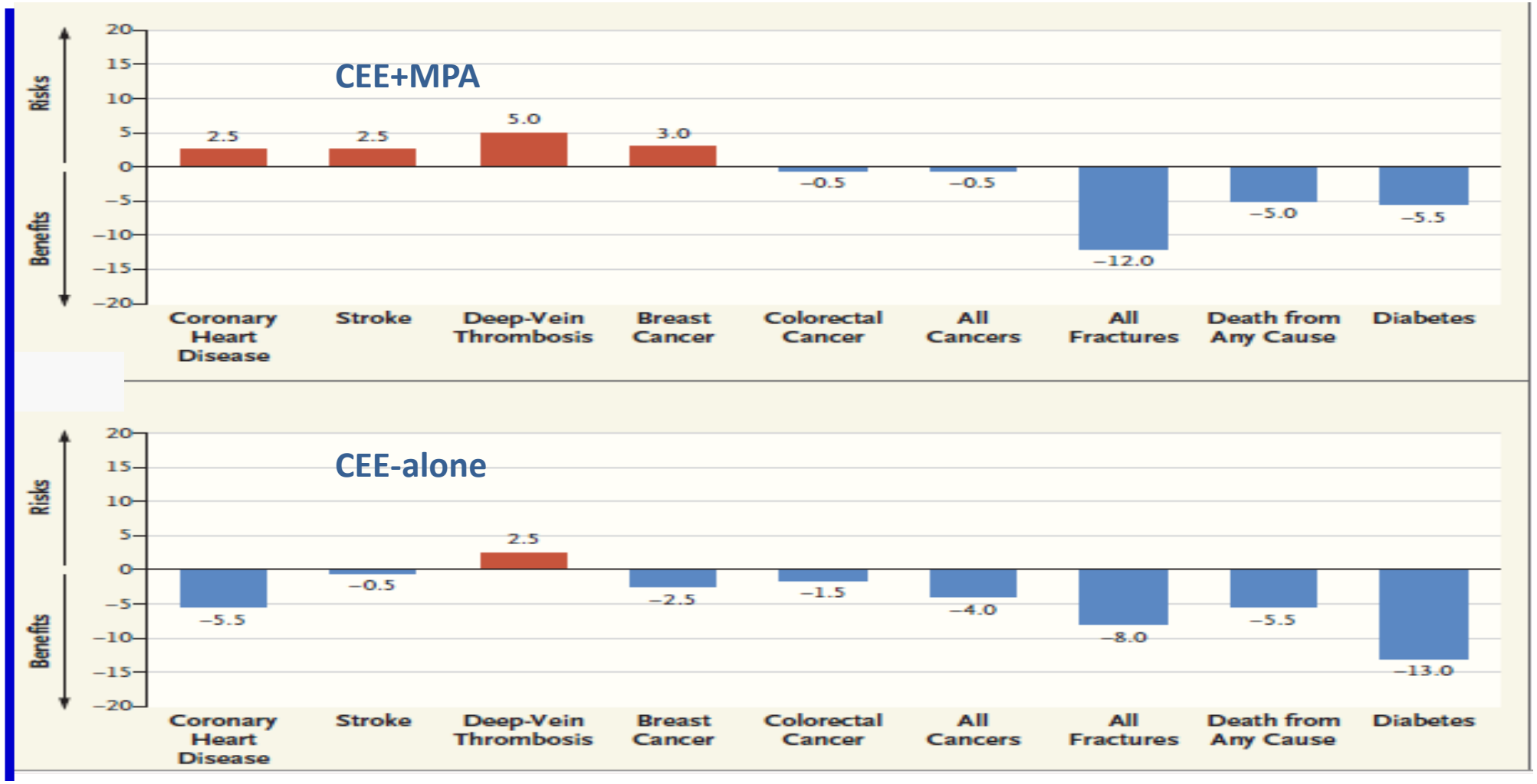
IMPORTANCE Menopausal hormone therapy continues in clinical use but questions remain regarding its risks and benefits for chronic disease prevention.

OBJECTIVE To report a comprehensive, integrated overview of findings from the 2 Women's

Manson JE, et al. *JAMA* 2013;310:1353-1368.

Benefits and Risks of MHT

Events per 1000 women age 50-59 per 5 y



Manson JE and Kaunitz AM. *N Engl J Med* 2016; 374:803-806; *intergroup difference in number of events*

JAMA The Journal of the American Medical Association

Research

18 year follow-up

JAMA | Original Investigation

Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality

The Women's Health Initiative Randomized Trials

JoAnn E. Manson, MD, DrPH; Aaron K. Aragaki, MS; Jacques E. Rossouw, MD; Garnet L. Anderson, PhD; Ross L. Prentice, PhD; Andrea Z. LaCroix, PhD; Rowan T. Chlebowski, MD, PhD; Barbara V. Howard, PhD; Cynthia A. Thomson, PhD; Karen L. Margolis, MD, MPH; Cora E. Lewis, MD, MSPH; Marcia L. Stefanick, PhD; Rebecca D. Jackson, MD; Karen C. Johnson, MD, MPH; Lisa W. Martin, MD; Sally A. Shumaker, PhD; Mark A. Espeland, PhD; Jean Wactawski-Wende, PhD; for the WHI Investigators

IMPORTANCE Health outcomes from the Women's Health Initiative Estrogen Plus Progestin and Estrogen-Alone Trials have been reported, but previous publications have generally not focused on all-cause and cause-specific mortality.

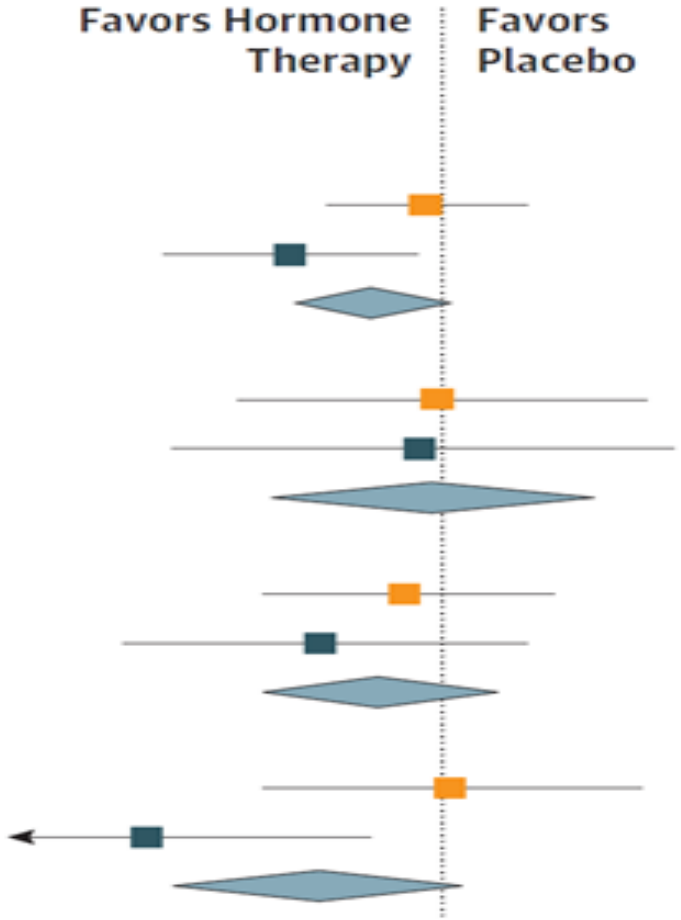
OBJECTIVE To examine total and cause-specific cumulative mortality, including during the

Manson JE, et al., for the WHI Investigators. *JAMA* 2017;318(10):927-938

Mortality Outcomes: Ages 50-59 y 18-Year Cumulative Follow-up

Cumulative Phase

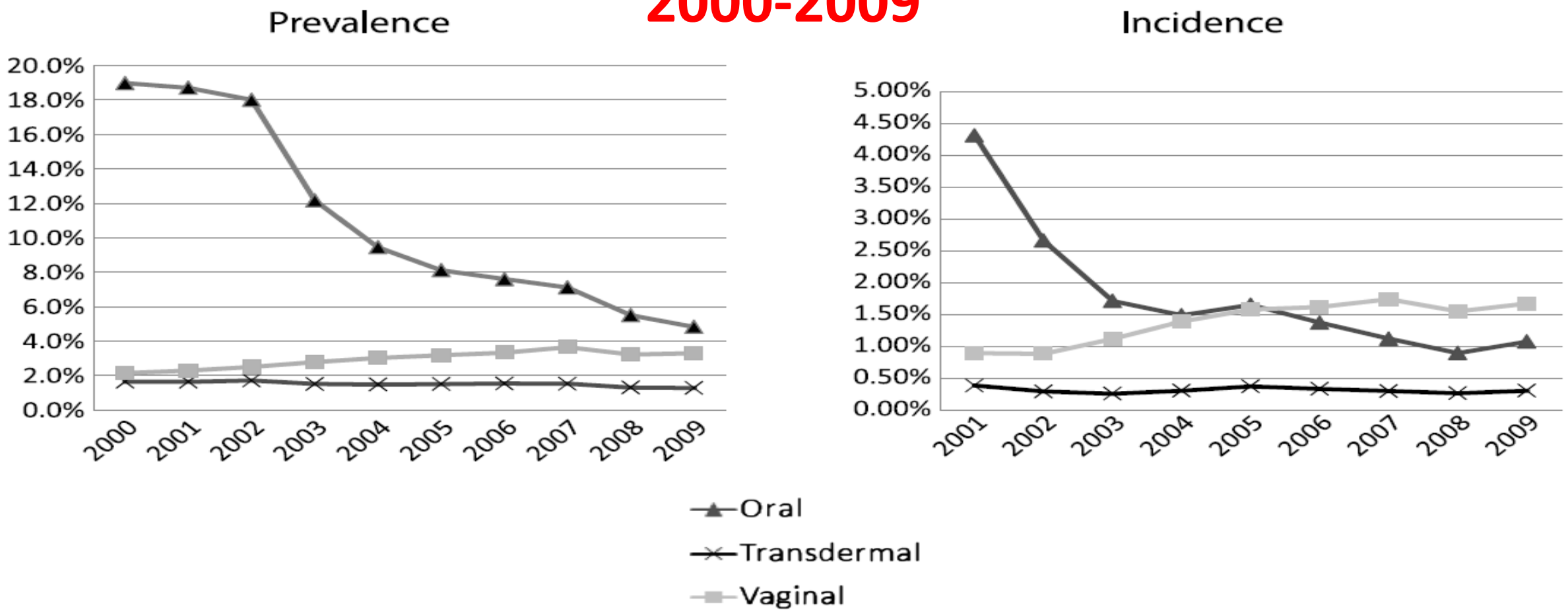
Outcome by Age	HR (95% CI)	*P* Value (Trend by Age)
Age 50-59 y		
All-cause mortality		
CEE plus MPA vs placebo	0.97 (0.83-1.14)	.17
CEE alone vs placebo	0.79 (0.64-0.96)	.18
Pooled trials	0.89 (0.79-1.01)	.06
CVD mortality		
CEE plus MPA vs placebo	0.99 (0.72-1.38)	.45
CEE alone vs placebo	0.97 (0.65-1.44)	.69
Pooled trials	0.98 (0.76-1.27)	.77
Cancer mortality		
CEE plus MPA vs placebo	0.94 (0.75-1.19)	.22
CEE alone vs placebo	0.83 (0.60-1.14)	.09
Pooled trials	0.90 (0.75-1.09)	.05
Other mortality		
CEE plus MPA vs placebo	1.01 (0.75-1.37)	.48
CEE alone vs placebo	0.63 (0.45-0.89)	.22
Pooled trials	0.82 (0.65-1.03)	.18



Manson JE, et al., for the WHI Investigators. *JAMA* 2017;318(10):927-938

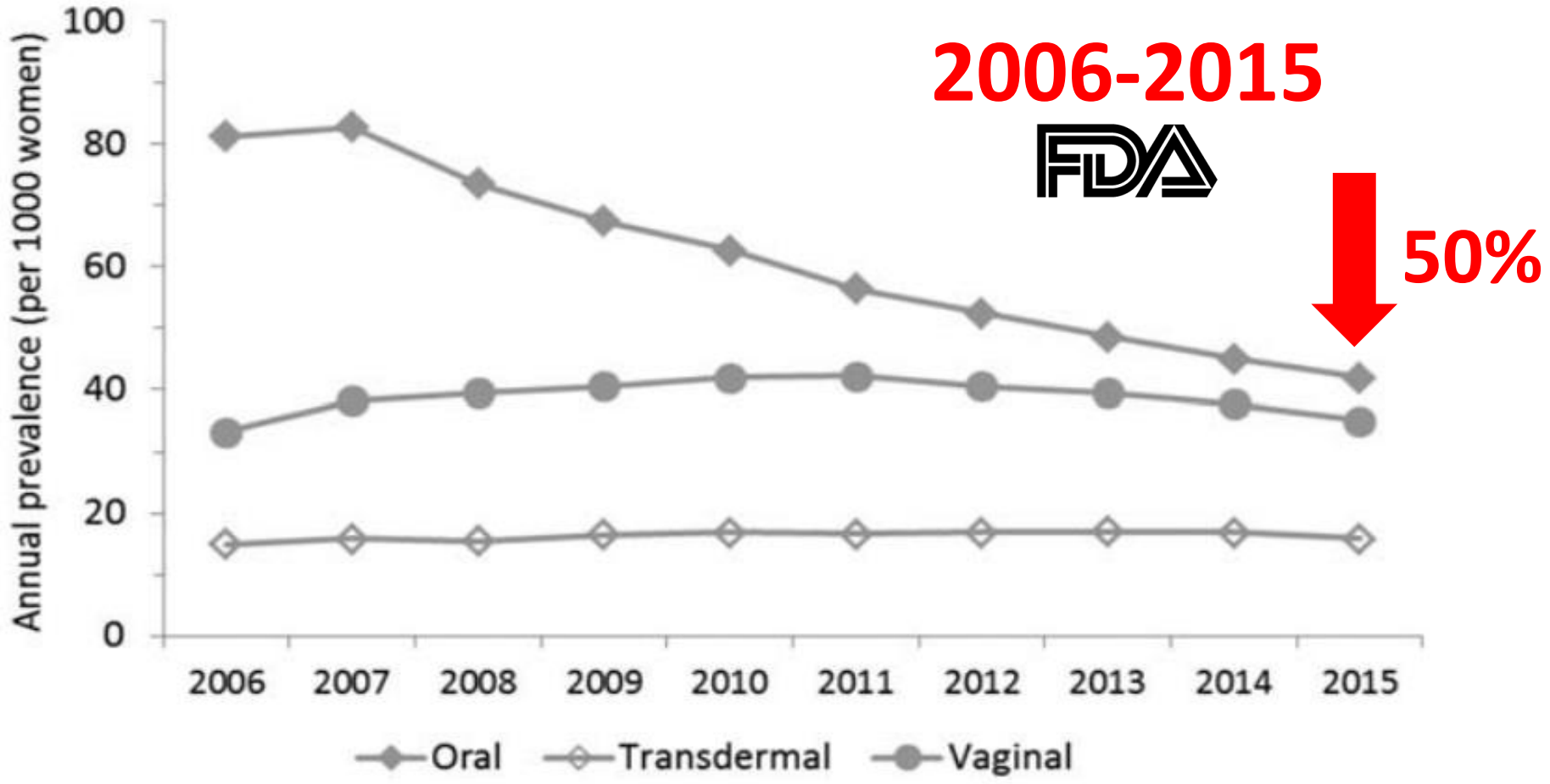
Hormone Therapy Prescriptions after the 2002 WHI Results…Women ≥ 50 y

2000-2009



Steinkellner AR, et al. *Menopause* 2012:19:616-621.

Trends in Noncontraceptive Estrogen Use among US Women ≥ 50 years with Commercial Health Insurance



Weissfeld JL, et al. *Menopause* 2018;25:611-614.

Current Trends: Use of cBHT

- The use of cBHT from compounding pharmacies is increasing among perimenopausal and postmenopausal women
- In contrast to FDA-approved therapies, trends in cBHT prescriptions have not historically been tracked
- Recent surveys provide evidence of prevalent use

Stuenkel CA and Manson JE. *JAMA Intern Med* 2017;177:1719-1720.

Current Trends: Use of cBHT

- Pharmacist survey[1]
  - 26-33 million cBHT prescriptions filled annually
  - Total sales estimated at $ 1.3 to 1.6 billion
- Patient surveys[2]
  - 1.0 to 2.5 million women ≥ 40 years of age used cBHT
  - 28 to 68% of all menopausal hormone therapy prescriptions filled annually
  - Revenues $ 1 to 2 billion
- Physician survey[3]
  - Recommend more by wellness physicians than other specialists
  - Emphasize cardiovascular/general health benefits

Stuenkel CA and Manson JE. *JAMA Intern Med* 2017;177:1719-1720; 1.Pinkerton JV and Constantine GD. *Menopause,* 2016; 23:359-367; 2.Pinkerton JV and Santoro N. *Menopause* 2015;22:926-936; 3. Constantine GD, et al. *Menopause* 2016;23:1075-82.

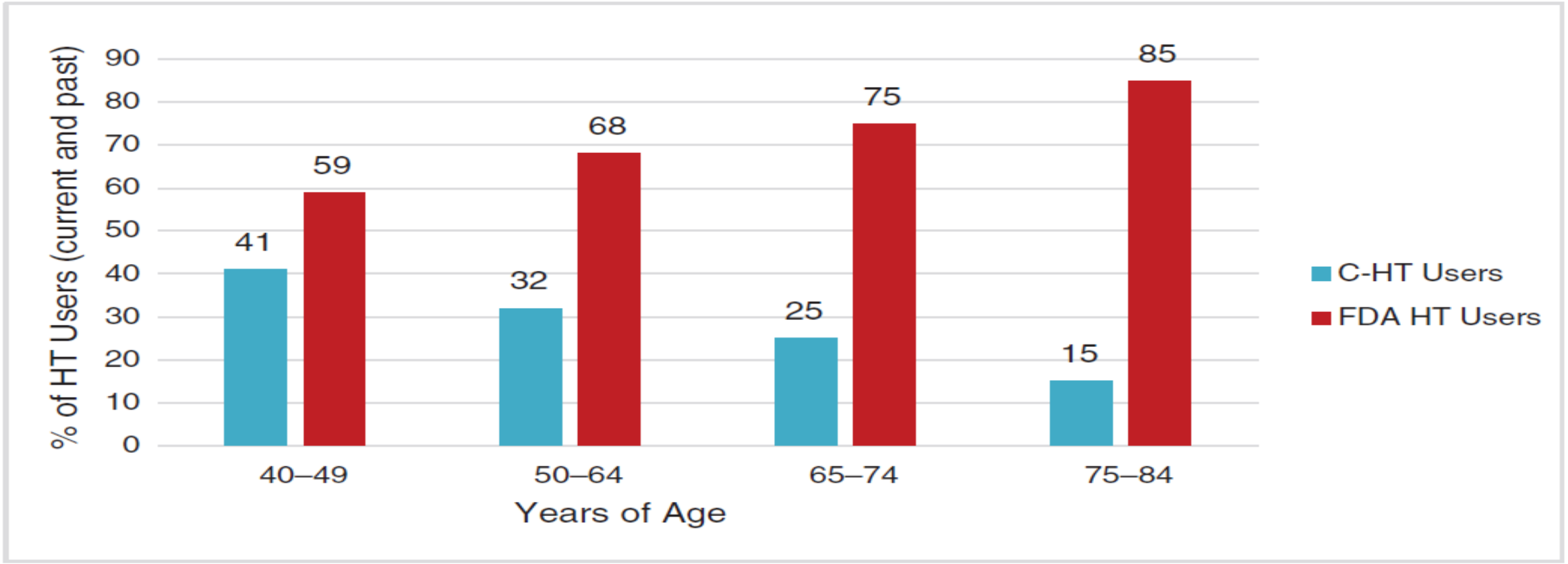
Current Trends: Use of cBHT

NAMS Patient survey

- 3,725 women surveyed
  - 9% currently taking menopausal hormone therapy
    - 1/3 of current users were taking cBHT
    - Of women ages 40 to 49, over 40% had used

Gass MLS, Stuenkel CA, Utian WH, et al. *Menopause* 2015;22:1276-84.

Use of Compounded HT in U.S.
North American Menopause Society Survey



Gass MLS, Stuenkel CA, Utian WH, et al. *Menopause* 2015;22:1276-84.

Thompson *et al. BMC Women's Health* (2017) 17:97
DOI 10.1186/s12905-017-0449-0

BMC Women's Health

RESEARCH ARTICLE Open Access

Why women choose compounded bioidentical hormone therapy: lessons from a qualitative study of menopausal decision-making

Jennifer Jo Thompson[1*], Cheryl Ritenbaugh[2] and Mark Nichter[3]

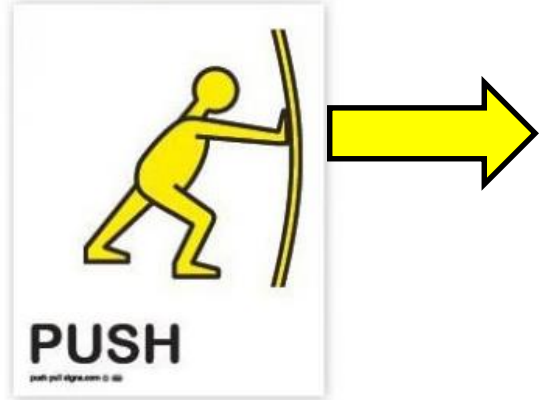
Abstract

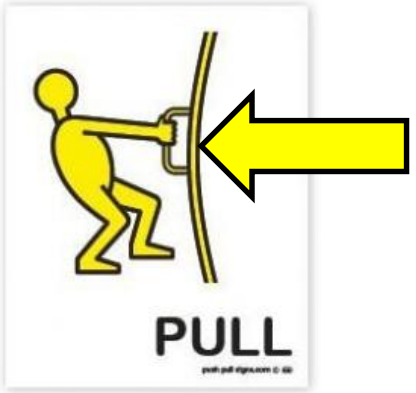
Background: In recent years, compounded bioidentical hormone therapy (CBHT) has emerged as a popular alternative to manufactured, FDA approved hormone therapy (HT)—despite concerns within the medical community and the availability of new FDA approved "bioidentical" products. This study aims to characterize the motivations for using CBHT in a U.S. sample of ordinary midlife women.

Thompson JJ, et al. *BMC Women's Health* 2017;17:97

Why Women Choose cBHT? The 'Push and Pull'

Motivations for using CBHT	# (%) of CBHT users
Push away from conventional therapies	
Fear and uncertainty about the safety of HT	17 (80.9%)
Distaste for conjugated estrogens, in particular	10 (47.6%)
Distrust of biomedicine and the pharmaceutical industry	20 (95.2%)
Push away from alternative therapies	
Ineffective symptom management	13 (61.9%)
Pull toward CBHT	
Effective symptom management	16 (76.2%)
Perception that CBHT is "safer" than conventional HT	16 (76.2%)
Desire for individualized treatment	12 (57.1%)
Enhanced clinical experience	13 (61.9%)





Thompson JJ, et al. *BMC Women's Health* 2017;17:97

Clinical Safety and Utility of cBHRT

- Compounding pharmacies play an important role for patients intolerant of FDA-approved therapies or for those not available
  - Sensitivity to a particular component
    - For example, patients with a peanut allergy
    - Peanut oil used in FDA-approved progesterone capsules
  - Requirements for a unique formulation not otherwise available
    - After PEPI trial, prior to FDA-approval of micronized progesterone
    - Testosterone therapy: no FDA-approved preparation for women; alternative: titrate FDA-approved therapies dosed for men

Stuenkel CA and Manson JE. *JAMA Intern Med* 2017;177:1719-1720; Mayo survey: relief of sexual symptoms 78% vs 33%, possibly because of inclusion of androgens. Iftikhar S, et al. *J Womens Health* 2011:20:559-65.

Compounded Hormone Therapies

- There is insufficient evidence regarding the safety and efficacy of compounded "bioidentical" hormone therapy for treatment of menopausal symptoms
- We were unable to identify any clinical trials comparing compounded hormone therapy for menopausal symptoms that met our criteria for inclusion
- Due to growing interest and an increase in prescription of compounded hormones, the limitations in the evidence base emphasizes the priority that should be given to future research

Grant MD, et al. *AHRQ Comparative Effectiveness Reviews*. 2015 Mar. pp 142-143.

Comparative Effectiveness Review
Number 147
Effective Health Care Program
Menopausal Symptoms: Comparative Effectiveness of Therapies

Compounded Hormone Therapies

- Many claims regarding the safety, efficacy, and superiority of compounded hormones have not been supported
- FDA has voiced concern over pharmacies misleading women and practitioners by unsupported claims of safety and greater efficacy than FDA-approved menopausal hormone therapies

Grant MD, et al. *AHRQ Comparative Effectiveness Reviews*. 2015 Mar. pp 142-143.

Clinical Safety and Utility of cBHRT

Concerns about cBHT products include:

- Lack of scientific evidence supporting claims of efficacy and safety
- Non-uniform dosing monitored by salivary hormone determinations
- Inconsistencies in manufacturing standards and state regulatory oversight
- Potential for product contamination and/or impurities
- **Lack of patient package inserts regarding anticipated risks**

Stuenkel CA and Manson JE. *JAMA Intern Med* 2017;177:1719-1720.

Clinical Safety and Utility of cBHRT

Inadvertent Cutaneous Transfer to Children and Pets

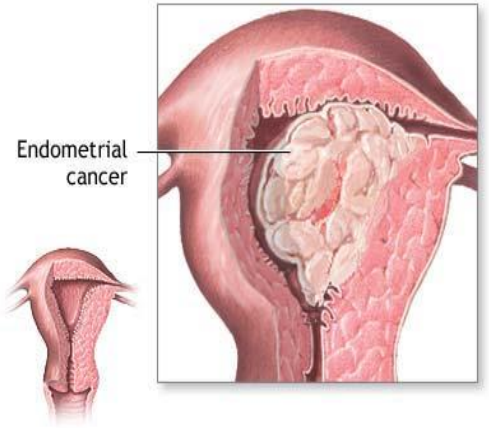
- Included in package labeling for some FDA-approved cutaneous estradiol and testosterone products following adverse event reporting of gynecomastia or virilization of exposed children
- Case reports of similar events in children exposed to cBHT creams[1-3]
- Transfer to pets can yield alopecia, nipple and labial enlargement leading to extensive evaluations and in some cases, repeat surgery to confirm successful neutering[4-7]

1.DePinho JC, et al. *J Reprod Med*, 2016;61:73-7; 2.Franklin SL. *Pediatr Endocrinol Rev* 2011;8:208-12;3.Felner EI and White PC. *Pediatrics* 2000;105:e55; 4.Schwarze RA, et al. JAVMA 2008;233:235-7; 5.Lau E. http://news.vin.com; 6.Stuenkel CA , et al. 2011 Endo Society P1-326; 7.Stuenkel CA et al. 2011 NAMS P85.

Clinical Safety and Utility of cBHRT

Endometrial Cancer: Potential Clinical Safety Issue

- Survey findings[1] and case reports[2] provide limited yet plausible evidence of increased endometrial cancer in women using cBHT as compared with women using FDA-approved therapies
- Additional concerns include:
  - Absence of randomized trials demonstrating safety of cBHT regarding endometrial cancer
  - **Lack of adverse event reporting by compounding pharmacies**



Stuenkel CA and Manson JE. *JAMA Intern Med* 2017;177:1719-1720; 1.Gass ML, *Menopause* 2015;22:1276-1284; 2.Pinkerton JV,Pickar JH. *Menopause* 2016;23:215-223.

Increased Incidence of Endometrial Cancer following the WHI: Assessment of Risk Factors

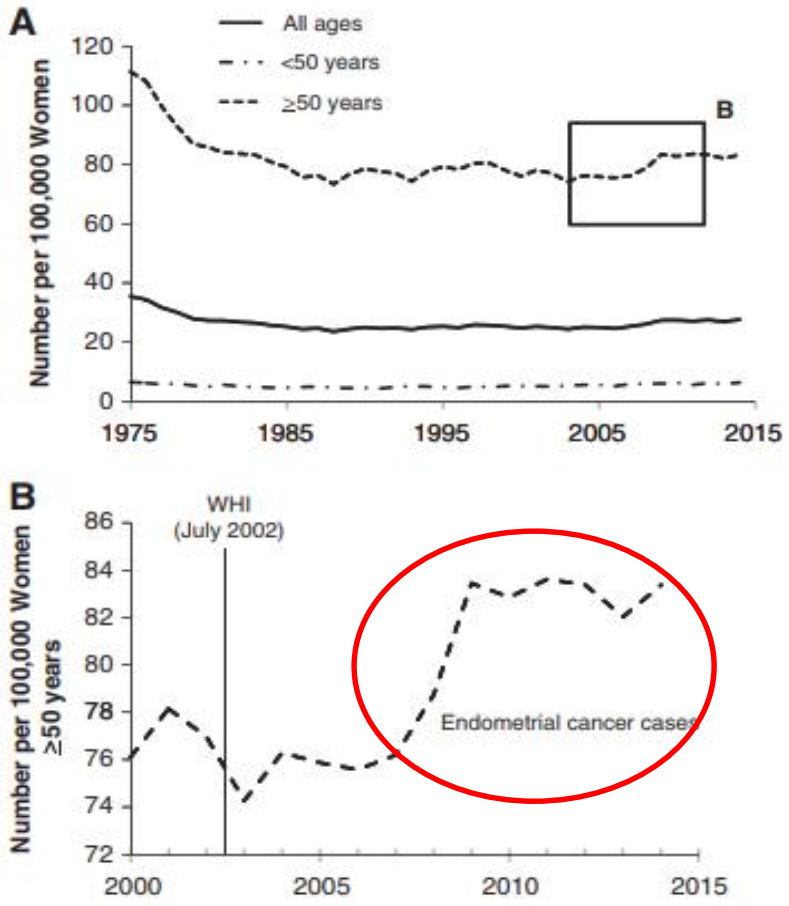


FIG. 1. Age-adjusted endometrial cancer incidence per 100,000 from SEER for **(A)** all women between 1975 and 2014 and **(B)** in women ≥50 years for 2000–2014.[4] SEER, Surveillance, Epidemiology, and End Result.

- In women 50-74 years, endometrial cancer rates:
  - 1992-2002 constant
  - 2006-2012 10% increase
- Possible contributing factors:
  - Decreased use of FDA-approved EPT
  - Increase in cBHT use
    - Potential for excess estrogen and inadequate progesterone
  - Prevalence of obesity and diabetes

Constantine GD, et al. *J Women's Health* 2019;28:237-243.

Clinical Safety and Utility of cBHRT vs. FDA-approved HT Products

- In surveys
  - Between 10%[1] and 50%[2] of women mistakenly thought cBHT was FDA-approved
  - 76% of respondents were uncertain[1]

Stuenkel CA and Manson JE. *JAMA Intern Med* 2017;177:1719-1720; 1.Pinkerton JV, Santoro N. *Menopause,* 2015;22:926-936; 2.Gass ML, et al. *Menopause* 2015;22:1276-1284.

Clinical Safety and Utility of cBHRT vs. FDA-approved HT Products

- Does the lack of a patient package insert regarding the cBHT medication's risks (which would be expected to be similar to the risks of FDA-approved hormones that come with a prominent 'black box' warning) contribute to this lack of awareness and a false sense of safety?

Stuenkel CA and Manson JE. *JAMA Intern Med* 2017;177:1719-1720.

JAMA Internal Medicine

VIEWPOINT

Compounded Bioidentical Hormone Therapy
Does the Regulatory Double Standard Harm Women?

Cynthia A. Stuenkel, MD
Department of Medicine, University of California, San Diego, School of Medicine, La Jolla.

JoAnn E. Manson, MD, DrPH
Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

By 2020, at least 50 million women in the United States will be postmenopausal, and the vast majority will have vasomotor symptoms (hot flashes) during the menopause transition and years beyond. The use of compounded bioidentical hormone therapy (cBHT) (**Table**), obtained from compounding pharmacies, is increasing among perimenopausal and postmenopausal women.[1-5] Virtually every medical society that provides guidance to clinicians treating women who are perimenopausal and postmenopausal recommends against prescribing cBHT. Instead, guidelines endorse judicious use of menopausal hormone therapy products regulated and approved by the US Food and Drug Administration (FDA).[1,2] This preference reflects concerns about cBHT prod-

Table. Systemic Menopausal Bioidentical Hormone Therapy Preparations[a]

Compounded BHT	Manufactured BHT Approved by the FDA
Estrogen[b]	
Estradiol	Estradiol oral tablets (0.5, 1.0, or 2.0 mg)
Estriol[c]	Estradiol transdermal patches (14, 25, 37.5, 50, 75, 100 µg)
Biestrogen (20% estradiol, 80% estriol)	Estradiol transdermal gels, emulsions, spray (doses range)
Triestrogen (10% estrone, 10% estradiol, 80% estriol)	Estradiol vaginal ring (provides 90-day systemic levels)
Progesterone[b]	Micronized progesterone oral capsules (100, 200 mg)
Combination therapies[d]	

Stuenkel CA and Manson JE. *JAMA Intern Med* 2017;177:1719-1720.

FDA-Approved 'Bioidenticals' for Menopausal Hormone Therapy

- Estrogen
  - Oral 17-*B* estradiol
  - Cutaneous 17-*B* estradiol preparations
    - Patches, gels, sprays, and emulsions
  - Vaginal estradiol preparations
    - Creams, ring, tablets, softgel 4 or 10 mcg capsules
- Progesterone
  - Oral micronized progesterone
- Combination therapy
  - Oral estradiol 1 mg/oral progesterone 100 mg softgel capsule

Stuenkel CA, et al. *J Clin Endocrinol Metab* 2015; 100:3975-4011

Choice of Menopausal Hormone Therapy

Custom-compounded hormones

We recommend using MHT preparations approved by the FDA and comparable regulating bodies outside the United States and recommend against the use of custom-compounded hormones. (Ungraded best practice statement)

Stuenkel CA, et al. *J Clin Endocrinol Metab* 2015; 100:3975-4011; Santoro N, et al. *J Clin Endocrinol Metab* 2016; 101:1318-1343.

Use of cBHT in Menopausal Women: An Opinion Statement of the Women's Health Practice and Research Network of the American College of Clinical Pharmacy

- Based on analysis of currently available research, this group endorses the position statements of other key organizations stating there is insufficient evidence to support the safety or efficacy of cBHT products over traditional HT products.
- cBHT cannot be recommended for women with menopausal symptoms as part of standard practice. Patients should be educated that bioidentical hormones are available in rigorously tested FDA-approved products in addition to cBHT.

McBane SE, et al. *Pharmacology* 2014;34:410-423.

Emergence and Clinical Utility of cBHRT Products Summary and Conclusions

- Historical perspective
  - Although the outcome of the WHI is attributed with catalyzing cBHT use, strategic efforts were underway well before 2002
- Major outcomes from the WHI
  - HT is currently indicated primarily to treat symptoms of menopause in recently menopausal women after cardiovascular and breast cancer risk assessment
- Current trends in use of cBHRT
  - Surveys indicate that use is prevalent with ~40% of younger women using cBHT
- Clinical safety and utility of cBHRT
  - In the absence of RCT for efficacy or safety, limited data underscore need for consistent, consolidated, and transparent adverse event reporting
- Comparison of safety and utility of cBHRT with FDA-approved HT
  - Product package labeling as required for all FDA-approved products would inform patients of anticipated risks with cBHT and state clearly that cBHT was not FDA-approved