

Hormone Therapy

Translating Research into Practice

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What is the Purpose of HT?

- Treat symptoms
- Prevent disease
- Improve quality of life

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Classic Symptoms

Vasomotor Symptoms

Vulvo-Vaginal Atrophy, Dryness,
Dyspareunia

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Proposed Benefits of Hormone Therapy 1990

Hot Flashes	Night Sweats
Vaginal Dryness	Moodiness
Anxiety	Tooth Loss
Pelvic Relaxation	Stress Incontinence
Sleep Quality	Alzheimer's Disease
Macular Degeneration	
Cardiovascular Disease	

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Lydia Pinkham's Vegetable Compound

Unicorn Root (*Aletris farinosa* L.) 8 oz.
Life Root (*Senecio aureus* L.) 6 oz.
Black Cohosh (*Cimicifuga racemosa* (L.) Nutt.) 6oz.
Pleurisy Root (*Asclepias tuberosa* L.) 6 oz.
Fenugreek Seed (*Trigonella foenum-graecum* L.) 12 oz.
Alcohol (18%) to make 100 pints

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LYDIA E. PINKHAM'S VEGETABLE COMPOUND.

Is a Positive Cure

for all these Painful Complaints and Weaknesses
accustomed to our best female population.
It will cure entirely the worst form of Female Com-
plaints, all ovarian troubles, Inflammation and Ulcera-
tion, Falling and Displacements, and the consequent
Spinal Weakness, and is particularly adapted to the
Change of Life.

It will dissolve and expel tumors from the uterus in
an early stage of development. The tendency to can-
cerous humors there is checked very speedily by its use.
It removes faintness, flatulency, destroys all craving
for stimulants, and relieves weakness of the stomach.
It cures Bloating, Headaches, Nervous Prostration,
General Debility, Sleeplessness, Depression and Indi-
gestion.

That feeling of bearing down, causing pain, weight
and backache, is always permanently cured by its use.
It will at all times and under all circumstances act in
harmony with the laws that govern the female system.
For the cure of Kidney Complaints of either sex this
Compound is unsurpassed.

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Lydia Pinkham's Vegetable Compound

Research: Herbal tradition

Randomized Controlled Trials: ???

Edward Adelbert Doisy - biochemist

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PREMARIN
0.625

1942

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Feminine Forever

Robert A. Wilson, MD

1966

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- menopausal castration amounts to a mutilation of the whole body
- The transformation, within a few years, of a formerly pleasant, energetic woman into a dull-minded but sharp-tongued caricature of her former self is one of the saddest of human spectacles.
- one must emphasize again and again that, by means of recently developed techniques of hormonal treatment, it is now possible to restore full femininity

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- Still another misconception concerning hormone therapy is the notion that estrogen predisposes toward cancer. The truth is exactly the opposite. There is increasing evidence that estrogen has a preventive effect on breast and genital cancers.

Wilson 1966

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David Reuban

- "As the estrogen is shut off, a woman comes as close as she can to being a man... To many women, the menopause marks the end of their useful life."

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Menopause Empowers

“The most creative force in the world is the postmenopausal woman with zest.”

Margaret Mead
American Anthropologist and Author
1901-1978

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HISTORICAL PERSPECTIVE

- 1942 Oral estrogens available
- 1966 Feminine Forever (Robert Wilson, M.D.)
- 1975 Increased endometrial CA (Smith, Ziel & Finkle)
- 1976-9 Progestogens protective (Gambrell, Hammond)
- 1985 Increased risk of heart disease (Wilson)
- 1987 Decreased risk of heart disease (Bush)

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INDICATIONS FOR USE (FDA)

	Estrogen
Vasomotor Symptoms	X
Vulvar and Vaginal Atrophy	X
Prevention of osteoporosis	X

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FDA Decision on Label Change

Advisory Committee voted in favor.
FDA medical officer Linda Golden recommended against label change.

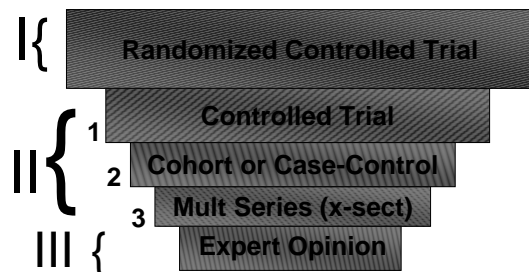
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- 1991-2 WHI designed

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Levels of Evidence



U.S. Preventive Services Task Force

HT Evidence

I **Randomized Controlled Trial**
 Hot flushes, maturation indices, surrogate endpoints: BMD, lipids, BP

II-2,3 **Cohort, Case-Control, Series**
 CVD, fractures, cognitive function, dementia, stroke, breast cancer, VTE

III **Expert Opinion**

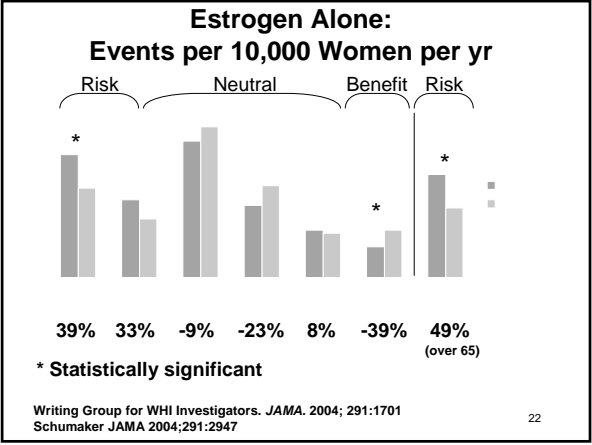
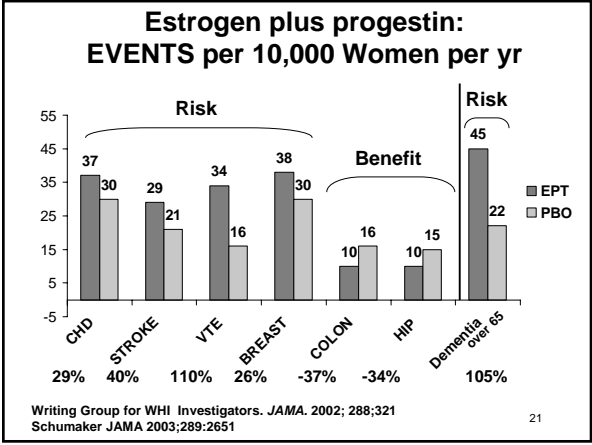
B O U N T I F U L !

The Purpose of WHI

To investigate strategies for the *prevention* and control of some of the most common causes of morbidity/mortality among postmenopausal women, including cancer, cardiovascular disease, and osteoporotic fractures

3 Arms of the Study

The Women's Health Initiative Study Group. *Control Clin Trials*. 1998;19(1):61



E-Along versus E+P (Baseline)

	CEE (5310)	E+P (8506)
Mean age (yrs)	63.6	63.3
BMI (kg/m ²)	30.1	28.5
1 st Birth at age <20 (%)	28.1	16.4
White (%)	75.5	83.9
Black (%)	14.7	6.5

The WHI Steering Committee. *JAMA* 2004; 291: 1701-1712
 Writing Group for WHI Investigators. *JAMA*. 2002; 288:321

E-Along versus E+P Placebo Event Rates

	CEE (5429)	E+P (8102)
Death rate	0.78	0.53
CHD rate	0.54	0.30
CHD death	0.16	0.06
Stroke	0.32	0.21
Global Index	1.90	1.15

The WHI Steering Committee. *JAMA* 2004; 291: 1701-1712
 Writing Group for WHI Investigators. *JAMA*. 2002; 288:321

Million Women Study

Effect of BMI and HT on Breast Cancer

BMI	<25	>25
EPT	2.31	1.78
ET	1.53	1.17

Lancet 2003;362:419

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Ethnicity and Breast Cancer

156,570 WHI participants

White, Black, Hispanic, Asian

Blacks' Breast Cancer HR 0.82

Whites' ER Negative CA 10%

Blacks' ER Negative CA 33%

OR 4.72 (3.18, 7.02)

Chlebowski *J Natl Cancer Inst* 97;433:2005

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WHI Conclusions

The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

Writing Group for WHI Investigators *JAMA* 2002; 288:321

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1995 PEPI Study: cholesterol benefit

1998 HERS: no benefit in secondary prevention of CVD

2002 WHI: not indicated for primary prevention of CVD

2002 Estrogen labeled a carcinogen

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The Disconnect

- WHI is a disease prevention study
- Majority of women seek hormones for control of symptoms

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INDICATIONS FOR USE (FDA)

	Estrogen
Vasomotor Symptoms	X
Vulvar and Vaginal Atrophy	X
Prevention of osteoporosis	X

Lowest dose
for the shortest amount of time

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ACOG Recommendation for Using HT for Prevention of Osteoporosis

I'm at high risk for osteoporosis. Can I continue on HT?

If you are also taking HT for treatment of menopausal symptoms, it may be appropriate. If you are taking HT solely for the prevention of osteoporosis, consider stopping it, because there are other medications that can help prevent osteoporosis and fractures that appear to carry lower risks for conditions such as breast cancer.

http://www.acog.org/from_home/publications/press_releases/nr10-01-04.cfm?printerFriendly=yes Accessed 4/04/05 31

ACOG Recommendations

So although the WHI clearly showed that hormones *should not* be used for disease prevention, they are still appropriate as a treatment for the relief of menopausal symptoms. As with all medications, the decision to use HT or ET is a personal one based on a review of the individual woman's health needs.

http://www.acog.org/from_home/publications/press_releases/nr10-01-04.cfm?printerFriendly=yes Accessed 3/30/05 32

USPSTF Recommendation

The U.S. Preventive Services Task Force (USPSTF) recommends against the routine use of estrogen and progestin for the prevention of chronic conditions in postmenopausal women.

USPSTF did not address the treatment of symptoms. The USPSTF concludes that the evidence is insufficient to recommend for or against the use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy.

<http://www.ahrq.gov/clinic/3rduspstf/hrt/hrtwh.htm> Accessed 3-31-05

North American Menopause Society Recommendations

Use of ET and EPT should be consistent with treatment goals, benefits, and risks for the individual woman, taking into account symptoms and domains (eg, sexuality, sleep) that may have an impact on quality of life.

Menopause 2004;11(6):589-600. 34

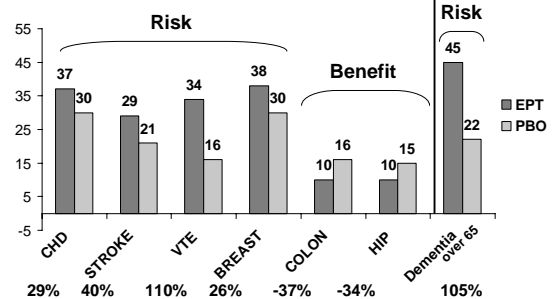
Annualized Percent Occurrence of Event by Age in Placebo Group

Composite

Age	VTE	Stroke	CVD	CA
50 - 59	0.06	0.08	0.13	0.26
60 - 69	0.19	0.20	0.28	0.36
70 - 79	0.27	0.44	0.60	0.41

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Estrogen plus progestin: EVENTS per 10,000 Women per yr



Writing Group for WHI Investigators. *JAMA*. 2002; 288:321
Schumaker *JAMA* 2003;289:2651

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Risks & Benefits of Aspirin per 10,000 participants

- 137 fewer heart attacks
- 39 fewer ischemic strokes
- 12 more hemorrhagic strokes

He JAMA 1998;280:1930

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Risks & Benefits of HT per 10,000 participants

E+P

More MIs (7), strokes (8), VTEs (18), dementia (23)

Fewer hip fractures (5), colon cancers (6)

E Alone

More VTEs (7), strokes (12), dementia (12)

Fewer hip fractures (6)

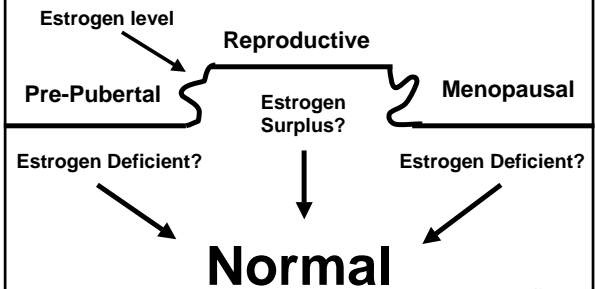
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Beta-Carotene & Retinol Trial CARET

- no chemopreventative benefits
- excess lung cancer & mortality
- consistent with other studies
- retraction of Vitamin E

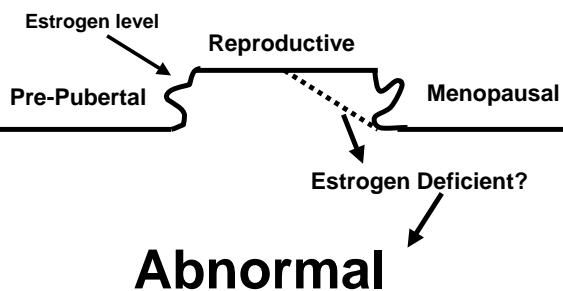
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Paradigm Shift



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Paradigm Shift



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Effect of Estrogen on Incontinence

Design: 27,347 in hormone arm of WHI

Endpoint: New incontinence and severity of pre-existing incontinence at one year

Results: Hormone therapy increased the risk of incontinence among those who were continent and worsened the incontinence in those who already had it

Hendrix JAMA 2005;293:935

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Hot Flashes after Stopping HT

Design: A survey of sexual function items was mailed to E+P trial participants 8-12 months after stopping study pills.

Results: 8405 responded (90%)
21.2% of HT users had hot flashes
4.8% of placebo users had hot flashes
OR: 5.9

Cochrane Abstract *Menopause 11:667, 2004*

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Sexual Function after Stopping HT

Design: A survey of sexual function items was mailed to E+P trial participants 8-12 months after stopping study pills.

Results: 8405 responded (90%) **41% of respondents to sexual function items reported sexual activity**

Gass Abstract *Menopause 11:667, 2004*

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Sexual Function after Stopping HT

- Most (~80%) reported no change in sexual function
- More former HT users reported less sexual desire, arousal, orgasm, satisfaction, and frequency of intercourse (20% vs 8%-9%)
greater vaginal tightness, painful intercourse, and lubricant use (15% vs 2-5%)

Gass Abstract *Menopause 11:667, 2004*

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Conclusions

- Translating research into practice?
 - a science and art requiring responsible logic
 - start with the best science, use good logic
 - relate above to patient's healthcare priorities
- Discuss the temporary nature of some symptoms
- Consider practical measures
- Discuss what to expect after stopping HT
- Low dose HT for a short amount of time
- Remain current on the topic and update the patient each year

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Dr. Gass - Questions & Answers

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